UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

HUMAN GENOME SCIENCES, INC., Plaintiff, v. GENENTECH, INC., Defendant.	Civil Action No. 08-166 (SLR)

DECLARATION OF A. ANTONY PFEFFER

I, A. Antony Pfeffer, hereby declare as follows:

1. I am an attorney-at-law of the State of New York and a member of Kenyon & Kenyon LLP, attorneys for plaintiff Human Genome Sciences, Inc.

2. Annexed hereto are true and correct copies of the following documents:

Exhibit A	Ni Substantive Motion 3 (To Change Benefit Accorded for the Contested Subject Matter), filed Dec. 7, 2005 in Interference No. 105,361.
Exhibit B	Declaration of John C. Reed, M.D., Ph.D. (Ni Exhibit 2064), filed in Interference No. 105,361.
Exhibit C	Excerpts from Adams Opposition 3 (Opposing Ni Substantive Motion 3), filed February 23, 2006 in Interference No. 105,361.
Exhibit D	Ni Reply 3, filed April 5, 2006 in Interference No. 105,361
Exhibit E	Joint Submission of Revised Transcript (Of July 27, 2006 Oral Argument)
Exhibit F	*Rasmusson v. SmithKline Beecham Corp.*, Inter. No. 104,646, Order Vacating O.C. and Entering Final Judgment (37 CFR 1.658) (B.P.A.I. Oct. 8, 2003)

Exhibit G	Ni Exhibit List, served September 14, 2006
Exhibit H	Title Page for the Deposition Transcript of Genentech expert, Michael Karin (Adams Exhibit 2064)
Exhibit I	Standing Order (Sept. 13, 2004) for Interference No. 105,361

I declare under penalty of perjury that the foregoing is true and correct.

A. ANTONY PFEFFER

DATED: June 26, 2008

EXHIBIT A

Paper ______

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Richard E. Schafer)

Human Genome Sciences, Inc.
Junior Party
(Patent 6,872,568;
Inventors: Jian Ni, Reiner L. Gentz, Guo-Liang Yu, Craig A. Rosen),

v.

Genentech, Inc.
Senior Party
(Application 10/423,448;
Inventors: Camellia W. Adams, Avi J. Ashkenazi, Anan Chuntharapai, Kyung Jin Kim).

Patent Interference No. 105,361 (RES)

NI SUBSTANTIVE MOTION 3
(To Change Benefit Accorded for the Contested Subject Matter)

I. Statement of Precise Relief Requested

Party Ni ("Human Genome Sciences" or "HGS") requests that the Board accord HGS the benefit of the following priority applications for the subject matter of counts 1 and 2 of the present interference and, contingent upon the granting of HGS's SUBSTANTIVE MOTION 4 TO SUBSTITUTE NEW COUNTS 3 AND 4, to accord HGS the benefit of the following priority applications for the subject matter of proposed counts 3 and 4:

- U.S. Provisional Appl. No. 60/040,846 (the "March 17, 1997 priority application");
- U.S. Provisional Appl. No. 60/054,021 (the "July 29, 1997 priority application");
- U.S. Appl. No. 09/042,583, filed March 17, 1998;
- U.S. Provisional Appl. No. 60/132,498, filed May 4, 1999;
- U.S. Provisional Appl. No. 60/133,238, filed May 7, 1999; and
- U.S. Provisional Appl. No. 60/148,939, filed August 13, 1999.

II. The Evidence

The evidence relied upon in support of this motion is set forth as Appendix A to this motion, which is attached hereto.

III. Statement of Material Facts

A statement of material facts in support of this motion is set forth as Appendix B to this motion, which is attached hereto.

IV. Argument

A. Overview

HGS's involved patent claims the benefit of six priority applications (Fact 1), as shown in Appendix C to this motion. In the Notice of Allowability for the application that resulted in HGS's involved patent, the Examiner explicitly acknowledged that the March 17, 1997 priority application enables and describes the agonistic and antagonistic antibodies specific for DR5 that are the subject of the two counts of this interference. (Fact 2). Nonetheless, HGS has not been accorded the benefit of any of its priority applications in this interference. (Fact 3). In this Motion, Party Ni will demonstrate beyond any question that HGS's priority applications, including its March 17, 1997 priority application, indeed fully enable and describe the contested subject matter of the present interference. Thus, HGS is entitled to the benefit of its priority applications.

The counts generally relate to antibodies that specifically bind to the extracellular domain (ECD) of a receptor molecule known alternatively as DR5, Apo-2, or TRAIL-R2. The amino acid sequence of DR5 is set forth in HGS's involved patent as SEQ ID NO: 2. (Fact 4). DR5 is a death domain-containing member of the tumor necrosis factor receptor (TNFR) superfamily (a "death receptor") and is involved in the induction of apoptosis in cells. (Fact 5). The antibodies of the counts are specified as being either antagonists (Count 1) or agonists (Count 2) of the DR5 protein. (Fact 6).

As explained in detail below, HGS's March 17, 1997 priority application, *inter alia*, (i) provides the complete amino acid sequence of DR5 (SEQ ID NO: 2), (ii) identifies the amino

acid residues that correspond to the ECD of DR5, (iii) recognizes that, because of the sequence similarity between DR5 and other death receptors, DR5 is also a death receptor, (iv) teaches methods for cloning, expressing and isolating DR5 and portions thereof (including the extracellular domain), (v) teaches methods for making and using agonistic and antagonistic antibodies (*e.g.*, monoclonal antibodies) that specifically bind to the extracellular domain of DR5, (vi) teaches methods for confirming that antibodies that specifically bind to the extracellular domain of DR5 are agonists or antagonists of DR5, and (vii) provides clear and practical uses for such antibodies.

Therefore, in view of the disclosure of the March 17, 1997 application and the advanced state of the art relating to the production of antibodies in general, as well as the production of agonistic and antagonistic antibodies against death receptors in particular, it is clear that HGS's March 17, 1997 priority application provides a fully enabled written description of the subject matter of counts 1 and 2 and of proposed counts 3 and 4.

HGS's later filed priority applications, including the July 29, 1997 application, include all of the information from the March 17, 1997 application and provide additional working examples confirming that DR5 induces apoptosis, (Fact 7), and that the extracellular domain of DR5 interacts with the apoptosis-inducing ligand TRAIL. (Fact 8). These examples reinforce the enablement and written description of antibodies that fall within the scope of counts 1 and 2 and of proposed counts 3 and 4. Thus, for at least the same reasons that HGS should be accorded the benefit of the March 17, 1997 priority application, HGS should also be accorded the benefit of its later filed priority applications.

B. The Legal Requirements for Being Accorded Benefit of an Earlier Application

Under 37 C.F.R. § 41.201, "accord benefit" is defined as Board recognition that a patent application provides a proper constructive reduction to practice under 35 U.S.C. § 102(g)(1). "Constructive reduction to practice means a described and enabled anticipation under 35 U.S.C. § 102(g)(1) in a patent application of the subject matter of a count." *Id.* Therefore, to be accorded the benefit of an earlier application for purposes of priority, a party need only have provided an enabled description of a single species within the scope of the count. *See Scripps Research Institute v. Genentech, Inc.*, 2005 WL 596764 (Bd. Pat. App. & Interf.) (citing *Hunt v. Treppschuh*, 523 F.2d 1389, 187 U.S.P.Q. 426, 429 (CCPA 1975)).

To satisfy the enablement requirement, the specification of a patent application must enable a person of ordinary skill in the art to make and use the claimed invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). A specification, however, need not enable information within the knowledge of an ordinary skilled artisan. *See Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254, 70 U.S.P.Q.2d 1321, 1325 (Fed. Cir. 2004). In the context of assessing the enablement requirement for monoclonal antibodies specifically, the court in *Wands* stated in its 1988 decision that "the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Wands*, 858 F.2d at 740, 8 U.S.P.Q.2d at 1406.

An application also must describe the subject matter of the count in terms that establish that the party was in possession of the invention, including all of the elements and limitations presented in the count, at the time of the earlier filing. *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 U.S.P.Q.2d 1128, 1131 (Fed. Cir. 1998). The descriptive text needed to satisfy the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 U.S.P.Q.2d 1078, 1084 (Fed. Cir. 2005).

The written description requirement can be met by: "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, or other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002)). In the context of satisfying the written description requirement for antibodies in particular, the Federal Circuit has recently stated that:

> based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim the antibody by its binding affinity to that described antigen.

Noelle v. Lederman, 355 F.3d 1343, 1349, 69 U.S.P.Q.2d 1508, 1514 (Fed. Cir. 2004).

C. HGS's March 17, 1997 Priority Application Provides an Enabled Description of an Embodiment of Counts 1 and 2 and of Proposed Counts 3 and 4

1. Counts 1 and 2

Count 1 is represented, in one alternative, by claim 21 of HGS's '568 patent. (Fact 9). Claim 21 (re-written in independent form with all the limitations of claim 15 from which it depends) is as follows:

> An isolated monoclonal antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2, wherein said antibody or fragment thereof is an antagonist of the protein of SEQ ID NO:2.

(Fact 10). Count 2, in one alternative, is represented by claim 20 of HGS's '568 patent. (Fact 11). Claim 20 is identical to claim 21, but recites an agonist rather than an antagonist. (Fact 12).

SEQ ID NO:2, common to both counts, is the amino acid sequence of the full-length DR5 protein. (Fact 13). Amino acid residues 1 to 133 of SEQ ID NO:2 represent the extracellular domain of DR5. (Fact 14). For simplicity, the counts will be referred to herein as being directed to antagonistic or agonistic antibodies or fragments thereof which specifically bind to the extracellular domain of DR5.

To be accorded benefit of the March 17, 1997 priority application, HGS need only show that the priority application enables and describes: (A) an antagonistic monoclonal antibody or fragment thereof that specifically binds to a protein consisting of the extracellular domain of

DR5 (Count 1); and (B) an agonistic monoclonal antibody or fragment thereof that specifically binds to a protein consisting of the extracellular domain of DR5 (Count 2). As explained below, the March 17, 1997 priority application provides a fully enabled description of antagonistic and agonistic antibodies of Counts 1 and 2.

(a) The Expert Opinion of Dr. John Reed

Party Ni has asked Dr. John Reed to evaluate the descriptions of HGS's priority documents in order to provide his opinion as to what a person of ordinary skill in the art would have understood upon reading the documents at the time of their filing. Dr. Reed's Declaration is specifically referenced in various places throughout this Motion. Dr. Reed is a highly recognized expert in the field of apoptosis and cell death regulation. He is currently the President and Chief Executive Officer of the Burnham Institute where he is also the head of a research laboratory. (Fact 15). Dr. Reed has authored or co-authored over 600 publications and has received several awards and honors from the scientific community (*e.g.*, the Decade's Most Highly Cited Apoptosis Researcher from 1991-2001, and the #1 Hottest Researcher in Life Sciences Worldwide (2000 and 1999)). (Fact 16). Dr. Reed's credentials and credibility are beyond challenge.

(b) Counts 1 and 2 are Fully Enabled

After reading HGS's March 17, 1997 priority application, a person of ordinary skill in the art would have been able to make and use, without undue experimentation, a monoclonal antibody that specifically binds to the extracellular domain of DR5 and that is an antagonist or an

agonist of DR5. As confirmed by Dr. Reed, to make and use an antibody of either count, one of ordinary skill in the art would typically: (1) produce monoclonal antibodies that specifically bind to the ECD of DR5; and (2) determine by routine screening whether the monoclonal antibodies are agonists or antagonists of DR5. (Fact 17). These two processes would not have involved undue experimentation at the time of filing.

(i) The March 17, 1997 Priority Application Indicates that DR5 is a Novel Apoptosis-Inducing Death Receptor

As confirmed by Dr. Reed, in view of HGS's March 17, 1997 application, including the disclosed similarity of DR5 to previously-known death receptors (TNFR1, Fas and DR3, each of which was known to induce apoptosis), and in view of the state of the art prior to March 17, 1997, the most reasonable conclusion to draw from HGS's March 17, 1997 application is that DR5 is expected, by persons of ordinary skill in the art, to be a novel death receptor. (Fact 18). Additionally, it is noted by Dr. Reed that, in view of HGS's March 17, 1997 application and the state of the art, a person of ordinary skill in the art would have predicted that activation of DR5 would induce apoptosis. (Fact 19). This conclusion is explicitly stated in Ni's March 17, 1997 application. (Fact 20). According to Dr. Reed, based on the information provided in HGS's March 17, 1997 application and what was known at the time, a person of ordinary skill in the art would have reasonably believed the assertion that activation of DR5 would induce apoptosis. (Fact 21).

(ii) Expression and Purification of DR5 Polypeptides Would Not Have Required Undue Experimentation

The March 17, 1997 priority application discloses the complete amino acid sequence of DR5, which is represented by SEQ ID NO:2. (Fact 22). The specification also identifies amino acid residues 52 to 184 as constituting the extracellular domain of DR5. (Fact 23). In HGS's subsequent applications, residues 52-184 are referred to as residues 1-133.[1] (Fact 25). The March 17, 1997 priority application also describes a cDNA sequence encoding the amino acid sequence of SEQ ID NO:2. (Fact 26). Also, a clone containing a cDNA encoding SEQ ID NO:2 was deposited at the American Type Culture Collection. (Fact 27). As confirmed by the Declaration of Dr. Reed, the DR5 cDNA described in the March 17, 1997 priority application could have been used to express the extracellular domain of DR5 in various expression systems. (Fact 28).

The March 17, 1997 priority application also teaches exemplary antigenic polypeptides and peptides for use in generating DR5-specific antibodies, including a polypeptide comprising amino acid residues from about 62 to about 110, and a polypeptide comprising amino acid residues from about 119 to about 164. (Fact 29). Both of these exemplary antigenic polypeptides include sequences within the DR5 extracellular domain. (Fact 30).

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[1] Subsequent to the March 17, 1997 application, the amino acids in SEQ ID NO:2 were renumbered in the sequence listing so that the residues of the leader sequence were designated -51 to -1, and the first residue of the extracellular domain was designated 1. (Fact 24). Therefore, amino acid residues 52 to 184 of SEQ ID NO:2 in the March 17, 1997 application are the same as amino acid residues 1 to 133 in the later applications and the involved '568 patent. (Fact 25). An illustration of the two numbering schemes is set forth in the attached Appendix D.

According to Dr. Reed, based on the description in HGS's March 17, 1997 application and knowledge in the art by March 17, 1997, expression of the extracellular domain of DR5 for the purposes of creating a purified protein for antibody production would have been routine to one of ordinary skill in the art. (Fact 31). In addition, Dr. Reed notes that, by using techniques that were routine by March 17, 1997, one of ordinary skill in the art could have purified the expressed DR5 polypeptide (or a fragment thereof) without undue experimentation. (Fact 32).

(iii) A Person of Ordinary Skill in the Art Could Have Made Monoclonal Antibodies that Specifically Bind the Extracellular Domain of DR5

With respect to making antibodies specific for DR5, the March 17, 1997 priority application states that:

> Antibodies according to the present invention may be prepared by any of a variety of methods using DR5 immunogens of the present invention. As indicated, such DR5 immunogens include the full length DR5 polypeptide (which may or may not include the leader sequence) and DR5 polypeptide fragments such as the ligand binding domain, the transmembrane domain, the intracellular domain and the death domain.

(Fact 33). As confirmed by Dr. Reed, techniques for producing monoclonal antibodies were well known in the art by March 17, 1997. (Fact 34). Dr. Reed notes that, in view of the March 17, 1997 priority application, persons of ordinary skill in the art could have, without undue experimentation, used such techniques to produce monoclonal antibodies that bind to the

extracellular domain of DR5. (Fact 35). Although monoclonal antibody technology involves screening hybridomas to identify those that secrete the desired antibody, such screening at the time of the March 17, 1997 priority application was considered routine in the art, as confirmed almost a decade earlier by the court in *Wands*. 858 F.2d at 740, 8 U.S.P.Q.2d at 1406.

(iv) A Person of Ordinary Skill in the Art Could Have Identified Agonistic and Antagonistic Antibodies Specific for the Extracellular Domain of DR5.

After making monoclonal antibodies that specifically bind to the extracellular domain of DR5, a person of ordinary skill in the art could have, as of the March 17, 1997 priority date, determined whether the antibodies were agonists or antagonists of DR5. As confirmed by Dr. Reed, and discussed below, such a determination could have been made without undue experimentation. (Fact 36).

Agonists are described in the March 17, 1997 priority application as "naturally occurring and synthetic compounds capable of enhancing or potentiating apoptosis." (Fact 37). Antagonists are described as "naturally occurring and synthetic compounds capable of inhibiting apoptosis." (Fact 38). Thus, as confirmed by Dr. Reed, a person of ordinary skill in the art would have simply needed to determine whether a particular monoclonal antibody that specifically binds to the extracellular domain of DR5, either (a) enhanced or potentiated apoptosis (agonistic) or (b) inhibited apoptosis (antagonistic). (Fact 39).

The March 17, 1997 priority application teaches an exemplary method for assaying for DR5-induced apoptosis and cites several scientific references that illustrate the general method.

(Fact 40). As summarized in this example, cells in which apoptosis is induced by DR5 expression become rounded and condensed and detach from the culture dish, which can be observed experimentally.

According to the Declaration of Dr. Reed, as of the March 17, 1997 priority date, a person of ordinary skill in the art would have understood that the apoptosis assay of this Example could have been conducted in the presence and absence of a candidate antibody. (Fact 41). If the addition of the antibody resulted in an *increase* in the extent of apoptosis as compared to the extent of apoptosis observed in the control experiment lacking the antibody, then a skilled person would conclude that the antibody was an *agonist* of DR5. (Fact 41). On the other hand, if the addition of the antibody resulted in a *decrease* in the extent of apoptosis as compared to the extent of apoptosis observed in the control experiment lacking the antibody, then a skilled person would conclude that the antibody was an *antagonist* of DR5. (Fact 41). As confirmed by Dr. Reed, conducting such screening experiments as of the March 17, 1997 priority date would not have required undue experimentation. (Fact 42).

An analysis of the factors set forth in *In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404, confirms the conclusion of Dr. Reed that making and using antibodies of the counts would not have involved undue experimentation. First, the nature of the invention is antagonistic and agonistic monoclonal antibodies. (Fact 6). The field of the invention was well-developed as of March 17, 1997. By March 17, 1997, others had demonstrated that agonistic and antagonistic monoclonal antibodies could be made that bind to the death receptors Fas and TNFR1, which are highly similar to DR5. (Fact 49). Thus, the state of the prior art was sufficiently advanced. A

person of ordinary skill in the art would have had knowledge of the scientific literature concerning TNFRs and at least a general familiarity with techniques involved in recombinant DNA, molecular biology and antibodies, including monoclonal antibodies. (Fact 43). A person of ordinary skill in the art would have had a Bachelor's degree or higher in the biological sciences. (Fact 43). Thus, the level of one of ordinary skill was high. Moreover, by March 17, 1997, others had made agonistic and antagonistic monoclonal antibodies specific for death receptors (Fact 49), and there is no indication that making such antibodies involved anything more than the application of routine techniques and screening. Thus, the level of predictability in the art was high. The March 17, 1997 priority application, in view of the existing knowledge in the art, provides all of the information necessary for one of ordinary skill in the art to make agonistic and antagonistic monoclonal antibodies of the counts, including, *inter alia*, the amino acid sequence of DR5, identification of the ECD, and sequence comparisons of DR5 to other death receptors. (Facts 22 and 23). Accordingly, the amount of direction provided by the March 17, 1997 priority application is substantial. In view of the substantial direction provided in the March 17, 1997 application, and the advanced state of the art, the absence of a working example in the application is immaterial. Finally, while making antibodies that fall within the scope of the counts would have involved some screening, just like in *Wands,* persons of ordinary skill in the art would have been prepared to engage in such screening. Therefore, the quantity of experimentation needed to make the antibodies of the counts, based on the March 17, 1997 application and the knowledge that existed in the art, would not have been undue.

In light of the foregoing considerations, balanced in view of what was known by March 17, 1997 and what is disclosed in HGS's March 17, 1997 priority application, screening for agonistic and antagonistic antibodies that bind to the ECD of DR5 would not have required undue experimentation.

(v) The "How to Use" Prong of 35 U.S.C. § 112, First Paragraph is Also Clearly Satisfied

The enablement requirement of 35 U.S.C. § 112, first paragraph, also includes a 'how to use' prong. This prong is satisfied if a person of ordinary skill in the art would have reasonably believed the applicant's assertion of utility. Because the March 17, 1997 priority application includes at least one believable asserted utility for the antibodies of each count, it is clear that the 'how to use' prong of 35 U.S.C. § 112, first paragraph is fully met for each count.

The specification describes therapeutic utilities for agonistic and antagonistic antibodies against DR5. More specifically, the specification teaches that agonistic monoclonal antibodies against the DR5 polypeptide are useful for treating diseases associated with increased cell survival or the inhibition of apoptosis, including cancers. (Fact 45). As noted by Dr. Reed, by March 17, 1997, persons of ordinary skill in the art reasonably expected that agonists of death receptors, including agonistic antibodies, could be used for treating cancers due to the well known ability of TNF-family death receptors to induce apoptosis of tumor cells. (Fact 46). The specification also indicates that antagonistic monoclonal antibodies against DR5 polypeptide, are useful for treating diseases associated with increased apoptosis, including AIDS/HIV infection. (Fact 47). As confirmed by Dr. Reed, by March 17, 1997, persons of ordinary skill in the art

reasonably expected that antagonists of death receptors, including antagonistic antibodies, could be used for treating various inflammatory diseases and HIV due to the well known role of TNF-family receptors in these diseases. (Fact 48). Thus, the above-noted therapeutic utilities set forth in the March 17, 1997 priority application would have been believable to persons of ordinary skill in the art.

In addition, as confirmed by Dr. Reed, monoclonal antibodies against TNFR1 and Fas, death receptors that share substantial sequence similarity with DR5, had been shown in the art to be agonists or antagonists of their respective receptors (*i.e.*, to induce or inhibit, respectively, the apoptotic signal induced by these receptors). (Fact 49). Thus, according to Dr. Reed, it would have been reasonable for one of ordinary skill in the art to believe that agonistic antibodies that specifically bind to DR5 would induce apoptosis of tumor cells and that antagonistic antibodies that specifically bind to DR5 would suppress apoptosis. (Fact 50). As confirmed by Dr. Reed, the above-mentioned therapeutic utilities of antagonistic and agonistic antibodies against DR5 asserted in HGS's March 17, 1997 priority application would have been regarded as believable by persons of ordinary skill in the art in view of what was known of the value of therapeutic agonistic or antagonistic antibodies that bind to apoptosis-inducing molecules. (Fact 51). The March 17, 1997 priority application therefore satisfies the 'how to use' prong of 35 U.S.C. § 112, first paragraph.

A second utility asserted in the March 17, 1997 application for antibodies against DR5 relates to diagnostic applications. (Fact 52). For example, the specification describes the use of antibodies to DR5 in assays for detecting over-expression of DR5 compared to normal control

tissue. (Fact 53). The Declaration of Dr. Reed confirms that the diagnostic utilities for DR5-specific antibodies asserted in the March 17, 1997 priority application would have been believable to one of ordinary skill in the art reading HGS's March 17, 1997 priority application. (Fact 54).

In summary, a person of ordinary skill in the art, in view of the March 17, 1997 specification and coupled with what was known in the art, could have made an isolated monoclonal antibody that specifically binds to the extracellular domain of DR5 and that is an antagonist or an agonist of DR5, without undue experimentation. Additionally, at least one utility for such antibodies asserted in the March 17, 1997 specification would have been believable to one of ordinary skill in the art for each count. Accordingly, it is clear that the March 17, 1997 priority application fully enables the subject matter of Counts 1 and 2.

(vi) The USPTO Has Explicitly Acknowledged That the March 17, 1997 Priority Application Enables and Describes Agonistic and Antagonistic Antibodies Specific for The ECD of DR5

Additionally, Party Ni respectfully reminds the Board that in the Notice of Allowability for the application that directly led to HGS's involved patent, the Examiner explicitly acknowledged that the March 17, 1997 priority application enables and describes agonistic and antagonistic antibodies specific for the ECD of DR5. (Fact 2). According to the Examiner:

> The structure of DR5 is shown in Fig. 1 of 60/040,846, with delineation of domains described in the Brief Description on page 5, lines 1-7, including the extracellular ligand-binding domain. It

> is also disclosed on page 32, lines 11-14, that DR5 agonists enhance apoptosis, and in Example 5 (pp. 43-44) that activation of DR5 is expected to result in induction of apoptosis. Therefore, with both the structure and the function of DR5 in hand, as well as a teaching of agonists and antagonists, which include antibodies (p. 29, lines 14-19 and p. 27, lines 16-17, respectively), the skilled artisan would have been able to make and use the instantly claimed agonist and antagonist antibody without undue experimentation and would have recognized the Inventors to be in possession of the claimed antibodies.

(Fact 2). Although the Board is not bound by the Examiner's statements, Party Ni respectfully urges the Board to consider the Examiner's position as further support for HGS's request to be accorded the benefit of the March 17, 1997 priority application.

(c) HGS's March 17, 1997 Priority Application Fully Describes the Inventions of Counts 1 and 2

As confirmed by the accompanying Declaration of John Reed, a person of ordinary skill in the art would recognize that the March 17, 1997 priority application fully describes the subject matter of Counts 1 and 2. (Fact 55). As discussed below, the March 17, 1997 priority application provides adequate written description of antibodies that fall within the scope of counts 1 and 2.

(i) The Sequence of DR5 and Its Extracellular Domain Are Described

The Federal Circuit has recently confirmed that disclosure of a fully characterized antigen will satisfy the written description requirement for antibodies specific to that antigen. *Noelle*, 355 F.3d at 1349, 69 U.S.P.Q.2d at 1514. The March 17, 1997 specification provides the complete sequence of DR5, including the portion of the sequence corresponding to the extracellular domain (amino acids 1-133), as recited in the counts. (Facts 22 and 23). The March 17, 1997 priority application fully characterizes the extracellular domain of DR5 (*e.g.*, by disclosing the amino acid residues of the DR5 protein that correspond to the extracellular domain: residues 52 to 184 (which in subsequent applications were re-numbered as residues 1-133)). Thus, under the *Noelle* analysis, the March 17, 1997 priority application adequately describes antibodies that specifically bind to the extracellular domain of DR5 by virtue of the identification and disclosure of the amino acid sequence of the DR5 extracellular domain.

The March 17, 1997 priority application also provides a detailed description of antigenic portions of DR5, which are "useful to raise antibodies, including monoclonal antibodies that bind specifically to a polypeptide of the invention." (Fact 56). The specification also provides examples of such polypeptides that fall within the ECD, including "a polypeptide comprising amino acid residues from about 62 to about 110 in Figure 1 (SEQ ID NO:2); [and] a polypeptide comprising amino acid residues from about 119 to about 164 in Figure 1 (SEQ ID NO:2) . . . ." (Fact 29).

As further confirmation that HGS had full possession of antibodies to the extracellular domain of DR5, the specification states that "polypeptide fragments such as the ligand binding domain" can be used as immunogens. (Fact 57). The "ligand binding domain" is identified as being within residues from about 52 to about 184 of SEQ ID NO:2 (*i.e.*, within the extracellular domain). (Fact 58).

(ii) Agonistic and Antagonistic Antibodies to the Extracellular Domain of DR5 are Described

As noted by Dr. Reed, the March 17, 1997 priority application provides a clear description of agonistic and antagonistic monoclonal antibodies that bind to the ECD of DR5. (Fact 59). By providing the amino acid sequence of the ECD of DR5, along with methods for producing and screening agonistic and antagonistic antibodies, HGS's March 17, 1997 priority application clearly sets forth the invention. (Fact 60). In view of the level of detail set forth in HGS's March 17, 1997 priority application regarding agonistic and antagonistic antibodies, a person of ordinary skill in the art could distinguish such antibodies from other agonistic and antagonistic monoclonal antibodies. (Fact 61). Thus, as noted by Dr. Reed, HGS's March 17, 1997 priority application clearly conveys to a person of ordinary skill in the art that the inventors had described monoclonal agonistic and antagonistic antibodies that specifically bind to the ECD of DR5, and that the inventors recognized that they had described such antibodies. (Fact 62).

The level of disclosure needed to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, varies depending on the state of the art. *See Capon*, 418 F.3d at 1357, 76 U.S.P.Q.2d at 1084. According to Dr. Reed, the state of the art as it existed by March 17, 1997

included demonstrations by others that agonistic and antagonistic antibodies could be made that bind to the death receptors Fas and TNFR1, which are highly similar to DR5. (Fact 63). In addition, as noted by Dr. Reed, monoclonal antibody technology was well-known to persons of ordinary skill in the art by March 17, 1997. (Fact 64). Thus, the state of the art relating to the production of monoclonal antibodies, including monoclonal antibodies against death receptors, was advanced and well developed by March 17, 1997. Accordingly, the disclosure set forth in the March 17, 1997 priority application is more than sufficient to describe the subject matter of counts 1 and 2.

2. *HGS's March 17, 1997 Priority Document Fully Describes and Enables Proposed Counts 3 and 4*

HGS has filed concurrently herewith SUBSTANTIVE MOTION 4 TO SUBSTITUTE NEW COUNTS 3 AND 4, requesting that counts 1 and 2 be replaced with proposed counts 3 and 4. The proposed modified counts are identical to counts 1 and 2 except that the limitation to monoclonal antibodies has been removed.

HGS's March 17, 1997 priority application also provides an enabled description of an embodiment of proposed counts 3 and 4. As explained above, HGS's March 17, 1997 priority application fully enables and describes isolated *monoclonal* antibodies that fall within the scope of counts 1 and 2. Such monoclonal antibodies necessarily fall within the scope of proposed counts 3 and 4, which are slightly broader than the existing counts.

In addition, the March 17, 1997 priority application enables and describes agonistic and antagonistic antibodies generally, and polyclonal antibodies in particular, wherein the antibodies

specifically bind the extracellular domain of DR5. For example, the March 17, 1997 priority application states that "[a]ntigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to *raise antibodies, including monoclonal antibodies*, that bind specifically to a polypeptide of the invention." (Fact 65). This passage clearly describes all types of antibodies for use with the invention. Furthermore, the application states that "preferred agonist[s] include *polyclonal* and monoclonal antibodies raised against the DR5 polypeptide, or a fragment thereof." (Fact 66). As confirmed by Dr. Reed, the March 17, 1997 application provides a clear description of polyclonal antibodies that bind to the ECD of DR5. (Fact 67).

Thus, HGS's March 17, 1997 priority application fully enables and describes agonistic and antagonistic antibodies that specifically bind to the extracellular domain of DR5, including monoclonal and polyclonal antibodies. Therefore, HGS's March 17, 1997 priority application fully enables and describes embodiments of proposed counts 3 and 4 for at least the same reasons that the application fully enables and describes embodiments of counts 1 and 2.

D. HGS's July 29, 1997 Priority Application Provides an Enabled Description of an Embodiment of Counts 1 and 2 and of Proposed Counts 3 and 4

1. Counts 1 and 2

HGS's July 29, 1997 priority application contains all of the disclosure found in HGS's March 17, 1997 application. (Fact 68). Therefore, the July 29, 1997 application would have fully enabled the invention of counts 1 and 2 for at least the same reasons that the March 17, 1997 application would have fully enabled the invention of counts 1 and 2.

In addition, as confirmed by Dr. Reed, HGS's July 29, 1997 application supplements the disclosure in Ni's March 17, 1997 application and also contains data that confirm various assertions made in the March 17, 1997 application. (Fact 69). For example, as acknowledged by Dr. Reed, the July 29, 1997 application provides a working example (Example 5) confirming that overexpression of DR5 in mammalian cells induces apoptosis. (Fact 70). Such an apoptosis assay, including the expected results, was prophetically described in Example 5 of the March 17, 1997 priority application. (Fact 71). Accordingly, the July 29, 1997 priority application provides more than an adequate written description of the subject matter of the counts.

HGS's July 29, 1997 priority application also provides a working example (Example 6) that confirms that the extracellular domain of DR5 binds the cytotoxic ligand TRAIL and blocks TRAIL-induced apoptosis. (Fact 72). Also, a DR5-Fc fusion construct was shown to inhibit TRAIL-induced apoptosis. (Fact 72).

As indicated by Dr. Reed, the results presented in the July 29, 1997 priority application confirm the teachings from HGS's March 17, 1997 application which identified DR5 as an apoptosis-inducing death receptor. (Fact 73). As confirmed by Dr. Reed, HGS's July 29, 1997 priority application provides further support for the asserted uses of agonistic and antagonistic antibodies that bind to the extracellular domain of DR5 as agents that either induce or inhibit DR5-mediated apoptosis. (Fact 74).

As noted above, the July 29, 1997 application contains all of the disclosure that is found in HGS's March 17, 1997 priority application. (Fact 68). Thus, the July 29, 1997 application

fully describes the invention of counts 1 and 2 for at least the same reasons that HGS's March 17, 1997 priority application fully describes the invention of counts 1 and 2. In addition, as confirmed by Dr. Reed, the working examples in the July 29, 1997 application provide further confirmation that the applicants adequately described an embodiment of counts 1 and 2. (Facts 73 and 74).

2. *Proposed Counts 3 and 4*

As with the March 17, 1997 priority application, HGS's July 29, 1997 priority application also provides an enabled description of an embodiment of proposed counts 3 and 4. As explained above, HGS's March 17 and July 29, 1997 priority applications fully enable and describe isolated agonistic and antagonistic antibodies that specifically bind to the extracellular domain of DR5, including monoclonal and polyclonal antibodies. Such antibodies necessarily fall within the scope of proposed counts 3 and 4. Therefore, HGS's July 29, 1997 priority application fully enables and describes embodiments of proposed counts 3 and 4 for at least the same reasons that the March 17 and July 29, 1997 priority applications fully enable and describe embodiments of counts 1 and 2.

E. *HGS's Later Filed Priority Applications Provide an Enabled Description of an Embodiment of Counts 1 and 2 and of Proposed Counts 3 and 4*

HGS's later filed priority applications (09/042,583, filed March 17, 1998; 60/132,498, filed May 4, 1999; 60/133,238, filed May 7, 1999; and 60/148,939, filed August 13, 1999) contain at least the same disclosure as is found in the March 17 and July 29, 1997 priority applications. Moreover, nothing in the later filed priority applications provides any basis for

doubting the assertions of the March 17, 1997 and July 29, 1997 priority applications. Thus, for at least the same reasons that the March 17 and July 29, 1997 priority applications enable and describe embodiments of counts 1 and 2 and of proposed counts 3 and 4, it follows that the later filed priority applications also enable and describe embodiments of counts 1 and 2 and of proposed counts 3 and 4.

V. Summary and Conclusion

HGS has not been accorded benefit of any of its priority applications. As demonstrated above and confirmed by Dr. Reed, Party Ni's priority applications fully describe and enable at least one embodiment of each of the existing counts and each of the proposed counts. Accordingly, HGS should be accorded the benefit of all of its priority applications (*see* Exhibit C), including, *inter alia*, the March 17, 1997 priority application and the July 29, 1997 priority application.

As discussed above, HGS's March 17, 1997 priority application would have enabled one of ordinary skill in the art to make and use, without undue experimentation, isolated monoclonal antibodies that specifically bind to a protein consisting of the extracellular domain of DR5 and that are antagonists or agonists of DR5. *Wands*, 858 F.2d at 740, 8 U.S.P.Q.2d at 1406. Furthermore, the March 17, 1997 priority application provides more than an adequate description of such antibodies and of the DR5 extracellular domain to which the antibodies specifically bind. *Noelle*, 355 F.3d at 1349, 69 U.S.P.Q.2d at 1514. Therefore, the March 17, 1997 priority application is a constructive reduction to practice of the inventions of counts 1 and 2 and of proposed counts 3 and 4. Indeed, in the Notice of Allowability for the application that directly

led to HGS's involved patent, the Examiner explicitly acknowledged that the March 17, 1997 priority application enables and describes agonistic and antagonistic antibodies specific for the ECD of DR5. It follows that the July 29, 1997 application, which provides working examples confirming that DR5 is an apoptosis-inducing, TRAIL-binding receptor, is also a constructive reduction to practice. It also necessarily follows that the March 17, 1998; May 4, 1999; May 7, 1999; and August 13, 1999 priority applications, which contain at least the same disclosure as is found in the March 17, 1997 and July 29, 1997 priority applications, are also constructive reductions to practice.

For at least the foregoing reasons, the Board should accord HGS benefit of its priority applications.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Jorge A. Goldstein, hereby certify that a copy of the foregoing NI SUBSTANTIVE MOTION 3 (To Change Benefit Accorded for the Contested Subject Matter), filed December 7, 2005, has been served on the attorney of record of Party Adams via Federal Express on this 7th day of December 2005, addressed as follows:

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APPENDIX A TO NI SUBSTANTIVE MOTION 3
(To Change Benefit Accorded for the Contested Subject Matter)

Evidence Relied on in the Motion

Ni Exhibit #	*NX #*	*Description*
Exhibit 2004	**NX 2004**	U.S. Patent No. 6,872,568
Exhibit 2018	**NX 2018**	Yagita *et al.*, *Cancer Sci. 95*:777-783 (2004) "TRAIL and its receptors as targets for cancer therapy"
Exhibit 2021	**NX 2021**	Sheridan *et al.*, *Science 277*:818-821 (August 8, 1997) "Control of TRAIL-induced Apoptosis by a Family of Signaling and Decoy Receptors"
Exhibit 2022	**NX 2022**	Pan *et al.*, *Science 277*:815-818 (August 8, 1997) "An Antagonist Decoy Receptor and a Death Domain-Containing Receptor for TRAIL"
Exhibit 2051	**NX 2051**	Maini et al., *Clin. Exp. Rheumatol.* 12 Suppl 11:S63-6 (1994)
Exhibit 2052	**NX 2052**	Feldmann et al., *Cir Shock* 43:179-84 (1994)
Exhibit 2053	**NX 2053**	Ware et al., *J. Cell Biochem*. 60:47-55 (1996)
Exhibit 2054	**NX 2054**	Ware et al., *The Cytokine Handbook, Chapter 20*, pgs. 549-550
Exhibit 2062	**NX 2062**	Ni U.S. Appl. No. 60/040,846 (March 17, 1997 priority application)
Exhibit 2063	**NX 2063**	Ni U.S. Appl. No. 60/054,021 (July 29, 1997 priority application)
Exhibit 2064	**NX 2064**	Declaration of John C. Reed, M.D., Ph.D.
Exhibit 2065	**NX 2065**	Chinnaiyan et al., *Science* 274:990-992 (1996)
Exhibit 2066	**NX 2066**	Marsters et al., *Current Biology* 6:1669-1676 (1996)
Exhibit 2067	**NX 2067**	Bodmer et al., *Immunity* 6:79-88 (1997)
Exhibit 2069	**NX 2069**	Notice of Allowability for U.S. Application No. 09/565,009, mailed January 21, 2005
Exhibit 2071	**NX 2071**	*Curriculum vitae* for Dr. John Reed
Exhibit 2072	**NX 2072**	Tartaglia and Goeddel, *J. of Biol. Chem*. 267: 4304-4307 (1992)

Ni Exhibit #	*NX #*	*Description*
Exhibit 2073	**NX 2073**	Ni File History for U.S. Appl. No. 09/042,583; (March 17, 1998 priority application)
Exhibit 2074	**NX 2074**	Ni File History for U.S. Appl. No. 60/132,498; (May 4, 1999 priority application)
Exhibit 2075	**NX 2075**	Ni File History for U.S. Appl. No. 60/133,238 (May 7, 1999 priority application)
Exhibit 2076	**NX 2076**	Ni File History for U.S. Appl. No. 60/148,939 (August 13, 1999 priority application)
Exhibit 2077	**NX 2077**	Locksley, RM, et al. *Cell* 104: 487, (2001)
Exhibit 2078	**NX 2078**	Tartaglia, LA *et al. Cell* 74: 845 (1993)
Exhibit 2079	**NX 2079**	Wallach, D. *et al. TIBS* 20: 342 (1995)
Exhibit 2080	**NX 2080**	Itoh *et al. J. Biol. Chem.* 268: 10932 (1993)
Exhibit 2081	**NX 2081**	Boldin, M.P. *et al. J Biol Chem* 270: 387 (1995)
Exhibit 2082	**NX 2082**	Kitson, J, *et al. Nature* 384: 372, (1996)
Exhibit 2083	**NX 2083**	Brutlag et al. *Comp. Appl. Biosci.* 6:237-245 (1990)
Exhibit 2084	**NX 2084**	Altschul et al., *J Mol Biol.* 215(3):403-10 (1990)
Exhibit 2085	**NX 2085**	Clewley et al., *Methods Mol Biol.* 70:119-29 (1997)
Exhibit 2086	**NX 2086**	Higgins et al., *Gene* 73(1):237-44 (1988)
Exhibit 2087	**NX 2087**	Devereux et al., *Nucleic Acids Res.* 12(1 Pt 1):387-95 (1984)
Exhibit 2088	**NX 2088**	Nakai and Kanehisa, *Genomics* 14:897-911, 1992
Exhibit 2089	**NX 2089**	Itoh, N. et al. Cell 66: 233 (1991)
Exhibit 2090	**NX 2090**	Yonehara, S *et al. J. Exp. Med.* 169: 1747 (1989)
Exhibit 2091	**NX 2091**	Trauth, B.C. *et al. Science* 245: 301 (1989)
Exhibit 2092	**NX 2092**	Cifone, MG *et al. J. Exp. Med.* 177: 1547 (1993)
Exhibit 2093	**NX 2093**	Tartaglia, L.A. *et al. Proc. Natl. Acad. Sci.* 88: 9292 (1991)
Exhibit 2094	**NX 2094**	Kohler and Milstein, *Nature* 256(5517):495-497 (1975)
Exhibit 2095	**NX 2095**	Espevik T. *et al. J. Exp. Med.* 171: 415 (1990)
Exhibit 2096	**NX 2096**	Engelmann, H. *et al. J. Biol. Chem.* 265: 14497 (1990)
Exhibit 2097	**NX 2097**	Sheehan, K.C.F. *et al. J. Exp. Med.* 181: 607 (1995)
Exhibit 2098	**NX 2098**	Fadeel, B. *et al. International Immunol.* 9: 201 (1997)
Exhibit 2099	**NX 2099**	Alderson, M.R. *et al. International Immunol.* 6: 1799 (1994)

APPENDIX B TO NI SUBSTANTIVE MOTION 3
(To Change Benefit Accorded for the Contested Subject Matter)

Statement of Material Facts

1. HGS's involved patent claims the benefit of six priority applications as outlined in Appendix C hereto. (Exhibit 2004, column 1, lines 6-17).

2. In the Notice of Allowability for the application that resulted in HGS's involved patent, the Examiner explicitly acknowledged that HGS's March 17, 1997 priority application (No. 60/040,846) enables and describes the agonistic and antagonistic antibodies specific for DR5 that are the subject of the two counts of this interference. (Exhibit 2069, page 2). The Examiner stated in the Notice of Allowability that:

> The structure of DR5 is shown in Fig. 1 of 60/040,846, with delineation of domains described in the Brief Description on page 5, lines 1-7, including the extracellular ligand-binding domain. It is also disclosed on page 32, lines 11-14, that DR5 agonists enhance apoptosis, and in Example 5 (pp. 43-44) that activation of DR5 is expected to result in induction of apoptosis. Therefore, with both the structure and the function of DR5 in hand, as well as a teaching of agonists and antagonists, which include antibodies (p. 29, lines 14-19 and p. 27, lines 16-17, respectively), the skilled artisan would have been able to make and use the instantly claimed agonist and antagonist antibody without undue experimentation

and would have recognized the Inventors to be in possession of the claimed antibodies.

(Exhibit 2069, page 2).

3. HGS has not been accorded the benefit of any of its priority applications in this interference. (Declaration of Interference No. 105,361, dated August 31, 2005, page 2).

4. The amino acid sequence of DR5 is set forth in HGS's involved patent as SEQ ID NO: 2. (Exhibit 2004, columns 141-143).

5. DR5 is a death domain-containing member of the tumor necrosis factor receptor (TNFR) superfamily (a "death receptor") and is involved in the induction of apoptosis in cells. (Exhibit 2018, page 777).

6. The antibodies of the counts are specified as being either antagonists (Count 1) or agonists (Count 2) of the DR5 protein. (Declaration of Interference No. 105,361, dated August 31, 2005, page 3; Exhibit 2004, column 159, lines 14-16, and 33-38).

7. HGS's July 29, 1997 priority application provides a working example indicating that DR5 induces apoptosis. (Exhibit 2063, page 48, line 17, through page 50, line 5; Exhibit 2064, paragraph 55).

8. HGS's July 29, 1997 priority application provides a working example indicating that the extracellular domain of DR5 interacts with the apoptosis-inducing ligand TRAIL. (Exhibit 2063, page 50, line 7, through page 51 line 2; Exhibit 2064, paragraph 56).

9. Count 1 is represented, in one alternative, by claim 21 of HGS's '568 patent. (Declaration of Interference No. 105,361, dated August 31, 2005, page 3).

10. Claim 21 of HGS's involved patent (re-written in independent form with all the limitations of claim 15 from which it depends) is as follows:

> An isolated monoclonal antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2, wherein said antibody or fragment thereof is an antagonist of the protein of SEQ ID NO:2.

(Exhibit 2004, column 159, lines 14-16 and 36-38).

11. Count 2, in one alternative, is represented by claim 20 of HGS's '568 patent. (Declaration of Interference No. 105,361, dated August 31, 2005, page 3).

12. Claim 20 of HGS's involved patent (re-written in independent form with all the limitations of claim 15 from which it depends) is as follows:

> An isolated monoclonal antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1

to 133 of SEQ ID NO:2, wherein said antibody or fragment thereof is an agonist of the protein of SEQ ID NO:2.

(Exhibit 2004, column 159, lines 14-16 and 33-35).

13. HGS's SEQ ID NO:2 is the amino acid sequence of the full-length DR5 protein. (Exhibit 2004, column 4, lines 53-54).

14. Amino acid residues 1 to 133 of HGS's SEQ ID NO:2 represent the extracellular domain of DR5. (Exhibit 2004, column 4, lines 57-60).

15. Dr. John Reed is currently the President and Chief Executive Officer of the Burnham Institute where he is also the head of a research laboratory. (Exhibit 2064, paragraphs 6 and 8).

16. Dr. Reed has authored or co-authored over 600 publications and has received several awards and honors from the scientific community including the Decade's Most Highly Cited Apoptosis Researcher from 1991-2001 and the #1 Hottest Researcher in Life Sciences Worldwide (2000 and 1999). (Exhibit 2064, paragraphs 10 and 11).

17. According to the Declaration of Dr. John Reed, to make and use an antibody that is an agonist or antagonist of DR5, one of ordinary skill in the art would typically: (1) produce monoclonal antibodies that specifically bind to the ECD of DR5; and (2) determine by routine screening whether the monoclonal antibodies are agonists or antagonists of DR5. (Exhibit 2064, paragraph 33).

18. The Declaration of Dr. John Reed indicates that, in view of HGS's March 17, 1997 application, including the disclosed similarity of DR5 to previously-known death receptors (TNFR1, Fas and DR3, each of which was known to induce apoptosis), and in view of the state of the art prior to March 17, 1997, the most reasonable conclusion to draw from HGS's March 17, 1997 application is that DR5 is expected, by persons of ordinary skill in the art, to be a novel death receptor. (Exhibit 2064, paragraph 32).

19. The Declaration of Dr. John Reed indicates that, in view of HGS's March 17, 1997 application and the state of the art, a person of ordinary skill in the art would have predicted that activation of DR5 would induce apoptosis. (Exhibit 2064, paragraph 32).

20. The conclusion that activation of DR5 would induce apoptosis is explicitly stated in Ni's March 17, 1997 application. (Exhibit 2062, page 6, lines 25-33; Exhibit 2064, paragraph 32).

21. The Declaration of Dr. John Reed indicates that, based on the information provided in HGS's March 17, 1997 application and what was known at the time, a person of ordinary skill in the art would have reasonably believed the assertion that activation of DR5 would induce apoptosis. (Exhibit 2064, paragraph 32).

22. HGS's March 17, 1997 priority application discloses the complete amino acid sequence of DR5, which is represented by SEQ ID NO:2, and shows a comparison of

the amino acid sequence of DR5 to other death receptors. (Exhibit 2062, page 5, lines 19-21, and Figures 1 and 2).

23. HGS's March 17, 1997 priority application identifies amino acid residues 52 to 184 of SEQ ID NO:2 as constituting the extracellular domain of DR5. (Exhibit 2062, page 5, lines 4-5, and Figure 1).

24. Subsequent to the filing of HGS's March 17, 1997 application, the amino acids in SEQ ID NO:2 were renumbered in the sequence listing so that the residues of the leader sequence were designated -51 to -1, and the first residue of the extracellular domain was designated 1. (Exhibit 2004, columns 141 through 143).

25. Residues 52-184 of SEQ ID NO:2 in HGS's March 17, 1997 priority application are the same as residues 1-133 referred to in HGS's involved patent, as shown in Appendix D hereto. (Exhibit 2062, page 5, lines 3-5, Figure 1).

26. HGS's March 17, 1997 priority application describes a cDNA sequence encoding the amino acid sequence of SEQ ID NO:2. (Exhibit 2062, page 5, lines 24-29, Figure 1).

27. A clone containing a cDNA encoding SEQ ID NO:2 was deposited at the American Type Culture Collection. (Exhibit 2062, page 3, lines 22-25, Figure 1).

28. The Declaration of Dr. John Reed indicates that the DR5 cDNA described in HGS's March 17, 1997 priority application could have been employed to express the

extracellular domain of DR5 in bacterial, yeast, insect and mammalian expression systems. (Exhibit 2064, paragraphs 36 and 41).

29. It is noted in HGS's March 17, 1997 priority application that "[n]on-limiting examples of antigenic polypeptides or peptides that can be used to generate DR5-specific antibodies include: a polypeptide comprising amino acid residues from about 62 to about 110 in Figure 1 (SEQ ID NO:2); a polypeptide comprising amino acid residues from about 119 to about 164 in Figure 1 (SEQ ID NO:2) . . . ." (Exhibit 2062, page 24, lines 24-28).

30. The exemplary antigenic polypeptides of HGS's March 17, 1997 priority application, comprising amino acid residues from about 62 to about 110, and from about 119 to about 164, include sequences within the DR5 extracellular domain. (Exhibit 2062, page 24, lines 24-28).

31. The Declaration of Dr. John Reed indicates that, based on the description in HGS's March 17, 1997 application and knowledge in the art by March 17, 1997, expression of the extracellular domain of DR5 for the purposes of creating a purified protein for antibody production would have been routine to one of ordinary skill in the art. (Exhibit 2064, paragraph 37).

32. The Declaration of Dr. John Reed indicates that, by using techniques that were routine by March 17, 1997, one of ordinary skill in the art could have purified the

expressed DR5 polypeptide (or a fragment thereof) without undue experimentation. (Exhibit 2064, paragraph 38).

33. The March 17, 1997 priority application states that:

> Antibodies according to the present invention may be prepared by any of a variety of methods using DR5 immunogens of the present invention. As indicated, such DR5 immunogens include the full length DR5 polypeptide (which may or may not include the leader sequence) and DR5 polypeptide fragments such as the ligand binding domain, the transmembrane domain, the intracellular domain and the death domain.

(Exhibit 2062, page 30, lines 26-31).

34. It is stated in the Declaration of Dr. John Reed that techniques for producing monoclonal antibodies were well known in the art by March 17, 1997. (Exhibit 2064, paragraph 40).

35. The Declaration of Dr. John Reed notes that, in view of the March 17, 1997 priority application, persons of ordinary skill in the art could have, without undue experimentation, used techniques that were known in the art to produce monoclonal antibodies that bind to the extracellular domain of DR5. (Exhibit 2064, paragraph 40).

36. The Declaration of Dr. John Reed states that it would not have required undue experimentation for a person of ordinary skill in the art to screen for agonistic antibodies that bind to the ECD of DR5; and that it would not have required undue experimentation for a person of ordinary skill in the art to screen for antagonistic antibodies that bind to the ECD of DR5. (Exhibit 2064, paragraph 45).

37. Agonists are described in HGS's March 17, 1997 priority application as "naturally occurring and synthetic compounds capable of enhancing or potentiating apoptosis." (Exhibit 2062, page 27, lines 18-19).

38. Antagonists are described in HGS's March 17, 1997 priority application as "naturally occurring and synthetic compounds capable of inhibiting apoptosis." (Exhibit 2062, page 27, lines 19-20).

39. It is stated in the Declaration of Dr. John Reed that a person of ordinary skill in the art, to identify agonistic and antagonistic antibodies that specifically bind to the ECD of DR5, would have needed to determine whether a particular monoclonal antibody that specifically binds to the extracellular domain of DR5, either (a) enhanced or potentiated apoptosis (agonistic) or (b) inhibited apoptosis (antagonistic). (Exhibit 2064, paragraph 42).

40. The March 17, 1997 priority application refers to an exemplary method (Example 5) for assaying for DR5-induced apoptosis and cites several scientific references that

illustrate the general method. (Exhibit 2062, page 43, line 11, through page 44, line 4).

41. It is stated in the Declaration of Dr. John Reed that, as of the March 17, 1997 priority date, a person of ordinary skill in the art would have understood that the apoptosis assay of Example 5 of the March 17, 1997 priority application (Exhibit 2062, page 43, line 11, through page 44, line 4) could have been conducted in the presence and absence of a candidate antibody, and that if the addition of the antibody resulted in an increase in the extent of apoptosis as compared to the extent of apoptosis observed in the control experiment lacking the antibody, then a person of ordinary skill in the art would have characterized the antibody as an agonist of DR5, and that if the addition of the antibody resulted in a decrease in the extent of apoptosis as compared to the extent of apoptosis observed in the control experiment lacking the antibody, then a person of ordinary skill in the art would have characterized the antibody as an antagonist of DR5. (Exhibit 2064, paragraph 43).

42. It is stated in the Declaration of Dr. John Reed that conducting screening experiments to determine if an antibody is an agonist or an antagonist of DR5, as of the March 17, 1997 priority date, would not have required undue experimentation. (Exhibit 2064, paragraph 43).

43. The Declaration of Dr. John Reed sets forth the following assertions regarding "undue experimentation" factors, as they apply to the invention of Counts 1 and 2: (A) *Nature*

of the Invention: The nature of the invention is monoclonal antibodies; monoclonal antibody technology was well-known to persons of ordinary skill in the art by March 17, 1997; (B) *State of the Prior Art*: By March 17, 1997, others had demonstrated that agonistic and antagonistic antibodies could be made that bind to the death receptors Fas and TNFR1, which are proteins that are highly similar to DR5; (C) *Level of One of Ordinary Skill*: The level of one of ordinary skill is high; a person of ordinary skill would have had a knowledge of the scientific literature concerning TNFRs, and more particularly the death receptors and their ligands; a person of ordinary skill would preferably have a Bachelor's degree or higher in the biological sciences and would have a general familiarity with techniques involved in recombinant DNA, molecular biology, and monoclonal antibodies; (D) *Level of Predictability in the Art*: the level of predictability in the art is high since one would have had a substantial degree of confidence in being able to produce agonistic and antagonistic antibodies that bind to a death receptor such as DR5; (E) *Amount of Direction Provided By the March 17, 1997 Priority Application*: The level of direction in the March 17, 1997 priority application is substantial since the application discloses the complete nucleotide and deduced amino acid sequences of DR5 and it indicates the location of the ECD and death domain of DR5, and also discloses the similarity of DR5 to other death receptors; (F) *Working Examples*: Although the March 17, 1997 priority application does not exemplify experiments that were actually carried out on agonistic and antagonistic antibodies, the absence of such examples would not prevent persons of ordinary skill in the art from obtaining and using such antibodies; and (G) *Quantity of*

Experimentation: Although a person of ordinary skill in the art would need to screen a number of antibodies to identify agonistic and antagonistic monoclonal antibodies that bind to the ECD of DR5, such screening would have been routine for a person of ordinary skill in the art by March 17, 1997; additionally, persons of ordinary skill in the art would have been prepared to screen a considerable number of antibodies to identify agonistic and antagonistic monoclonal antibodies that bind to the ECD of DR5, and such a person would have been able to distinguish such agonistic antibodies from antagonistic antibodies. (Exhibit 2064, paragraph 35(a)-(g), emphasis added).

44. It is noted in the Declaration of Dr. John Reed that, based on what was known by March 17, 1997 and what is disclosed in HGS's March 17, 1997 priority application, screening for agonistic and antagonistic antibodies that bind to the ECD of DR5 would not have required undue experimentation. (Exhibit 2064, paragraph 45).

45. HGS's March 17, 1997 priority application indicates that DR5 agonists, including agonistic monoclonal antibodies against the DR5 polypeptide, are useful for treating diseases associated with increased cell survival or the inhibition of apoptosis, including cancers. (Exhibit 2062, page, lines 27-33; page 27, lines 3-10).

46. It is noted in the Declaration of Dr. John Reed that, by March 17, 1997, persons of ordinary skill in the art reasonably expected that agonists of death receptors, including agonistic antibodies, could be used for treating cancers due to the well

known ability of TNF-family death receptors to induce apoptosis of tumor cells. (Exhibit 2064, paragraph 23).

47. HGS's March 17, 1997 priority application indicates that DR5 antagonists, including antagonistic monoclonal antibodies against DR5 polypeptide, are useful for treating diseases associated with increased apoptosis, such as AIDS/HIV infection. (Exhibit 2062, page 26, line 34, though page 27, line 2; page 27, lines 11-17; page 31, lines 10-36).

48. It is noted in the Declaration of Dr. John Reed that, by March 17, 1997, persons of ordinary skill in the art reasonably expected that antagonists of death receptors, including antagonistic antibodies, could be used for treating various inflammatory diseases and HIV due to the well known role of TNF-family receptors in these diseases. (Exhibit 2064, paragraph 23 and 51).

49. It is noted in the Declaration of Dr. John Reed that monoclonal antibodies against TNFR1 and Fas, death receptors that share substantial sequence similarity with DR5, had been shown in the art to be agonists or antagonists of their respective receptors (*i.e.*, to induce or inhibit, respectively, the apoptotic signal induced by these receptors). (Exhibit 2064, paragraphs 35(b) and 49).

50. It is noted in the Declaration of Dr. John Reed that it would have been reasonable for one of ordinary skill in the art to believe that agonistic antibodies that specifically bind to DR5 would induce apoptosis of tumor cells and that antagonistic antibodies

that specifically bind to DR5 would suppress apoptosis. (Exhibit 2064, paragraph 50).

51. It is noted in the Declaration of Dr. John Reed that the therapeutic use of agonistic antibodies in methods for treating cancers, and the therapeutic use of antagonistic antibodies for treating inflammatory diseases, such as rheumatoid arthritis, and HIV, would have been believable to one of ordinary skill in the art reading HGS's March 17, 1997 priority application in view of what was known of the value of therapeutic agonistic or antagonistic antibodies that bind to apoptosis-inducing molecules. (Exhibit 2064, paragraph 51).

52. HGS's March 17, 1997 application discloses diagnostic uses for antibodies against DR5. (Exhibit 2062, page 25, line 16, through page 26, line 2).

53. HGS's March 17, 1997 priority application refers to a diagnostic assay for detecting over-expression of DR5 compared to normal control tissue. (Exhibit 2062, page 25, lines 20-22).

54. It is noted in the Declaration of Dr. John Reed that HGS's March 17, 1997 priority application describes diagnostic uses for antibodies to DR5, and that such uses would have been believable to one of ordinary skill in the art reading HGS's March 17, 1997 priority application. (Exhibit 2064, paragraph 52).

55. It is noted in the Declaration of John Reed that HGS's March 17, 1997 application provides a clear description of polyclonal antibodies and agonistic and antagonistic monoclonal antibodies that bind to the ECD of DR5. (Exhibit 2064, paragraph 48).

56. It is noted in HGS's March 17, 1997 priority application that "[a]ntigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies that bind specifically to a polypeptide of the invention" and discloses exemplary antigenic polypeptides (Exhibit 2062, page 24, lines 16-32).

57. It is noted in HGS's March 17, 1997 priority application that "polypeptide fragments such as the ligand binding domain" can be used as immunogens. (Exhibit 2062, page 30, lines 26-31).

58. The "ligand binding domain" is identified in HGS's March 17, 1997 priority application as being within residues from about 52 to about 184 of SEQ ID NO:2 (*i.e.*, within the extracellular domain). (Exhibit 2062, page 23, lines 20-22).

59. It is noted in the Declaration of Dr. John Reed that the March 17, 1997 priority application provides a clear description of agonistic and antagonistic monoclonal antibodies that bind to the ECD of DR5. (Exhibit 2064, paragraph 48).

60. It is noted in the Declaration of Dr. John Reed that, by providing the amino acid sequence of the ECD of DR5, along with methods for producing and screening

agonistic and antagonistic antibodies, HGS's March 17, 1997 priority application clearly sets forth the invention. (Exhibit 2064, paragraph 48).

61. It is noted in the Declaration of Dr. John Reed that, in view of the level of detail set forth in HGS's March 17, 1997 priority application regarding agonistic and antagonistic antibodies, a person of ordinary skill in the art could distinguish such antibodies from other agonistic and antagonistic monoclonal antibodies. (Exhibit 2064, paragraph 48).

62. It is noted in the Declaration of Dr. John Reed that HGS's March 17, 1997 priority application clearly conveys to a person of ordinary skill in the art that the inventors had described monoclonal agonistic and antagonistic antibodies that specifically bind to the ECD of DR5, and that the inventors recognized that they had described such antibodies. (Exhibit 2064, paragraph 48).

63. It is stated in the Declaration of Dr. John Reed that the state of the art as it existed by March 17, 1997 included demonstrations by others that agonistic and antagonistic antibodies could be made that bind to TNFR family members Fas and TNFR1, which are highly similar to DR5. (Exhibit 2064, paragraph 35b).

64. It is stated in the Declaration of Dr. John Reed that monoclonal antibody technology was well-known to persons of ordinary skill in the art by March 17, 1997. (Exhibit 2064, paragraphs 35a and 40).

65. It is noted in HGS's March 17, 1997 priority application that "[a]ntigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention." (Exhibit 2062, page 24, lines 16-18).

66. It is noted in HGS's March 17, 1997 priority application that "preferred agonist[s] include polyclonal and monoclonal antibodies raised against the DR5 polypeptide, or a fragment thereof." (Exhibit 2062, page 29, lines 14-15, emphasis added).

67. It is stated in the Declaration of Dr. John Reed that the March 17, 1997 application provides a clear description of polyclonal antibodies that bind to the ECD of DR5. (Exhibit 2064, paragraph 48).

68. HGS's July 29, 1997 priority application (No. 60/054,021 (Exhibit 2063)) contains all of the disclosure found in HGS's March 17, 1997 application (No. 60/040,846). (Exhibit 2062).

69. It is stated in the Declaration of Dr. John Reed that HGS's July 29, 1997 application supplements the disclosure in HGS's March 17, 1997 application and also contains data that confirm various assertions made in the March 17, 1997 application. (Exhibit 2064, paragraph 54).

70. HGS's July 29, 1997 application provides a working example (Example 5) showing that overexpression of DR5 in mammalian cells induces apoptosis. The specification,

including Figures 5A and 5B, shows that overexpression of DR5 induced apoptosis in MCF7 and HeLa cells to a similar extent as overexpression of TNFR1. (Exhibit 2064, paragraph 54; Exhibit 2063, page 48, line 17, through page 50, line 5).

71. Example 5 of HGS's July 29, 1997 priority application was prophetically described in Example 5 of HGS's March 17, 1997 priority application. (Exhibit 2063, page 43, line 10, through page 44, line 4).

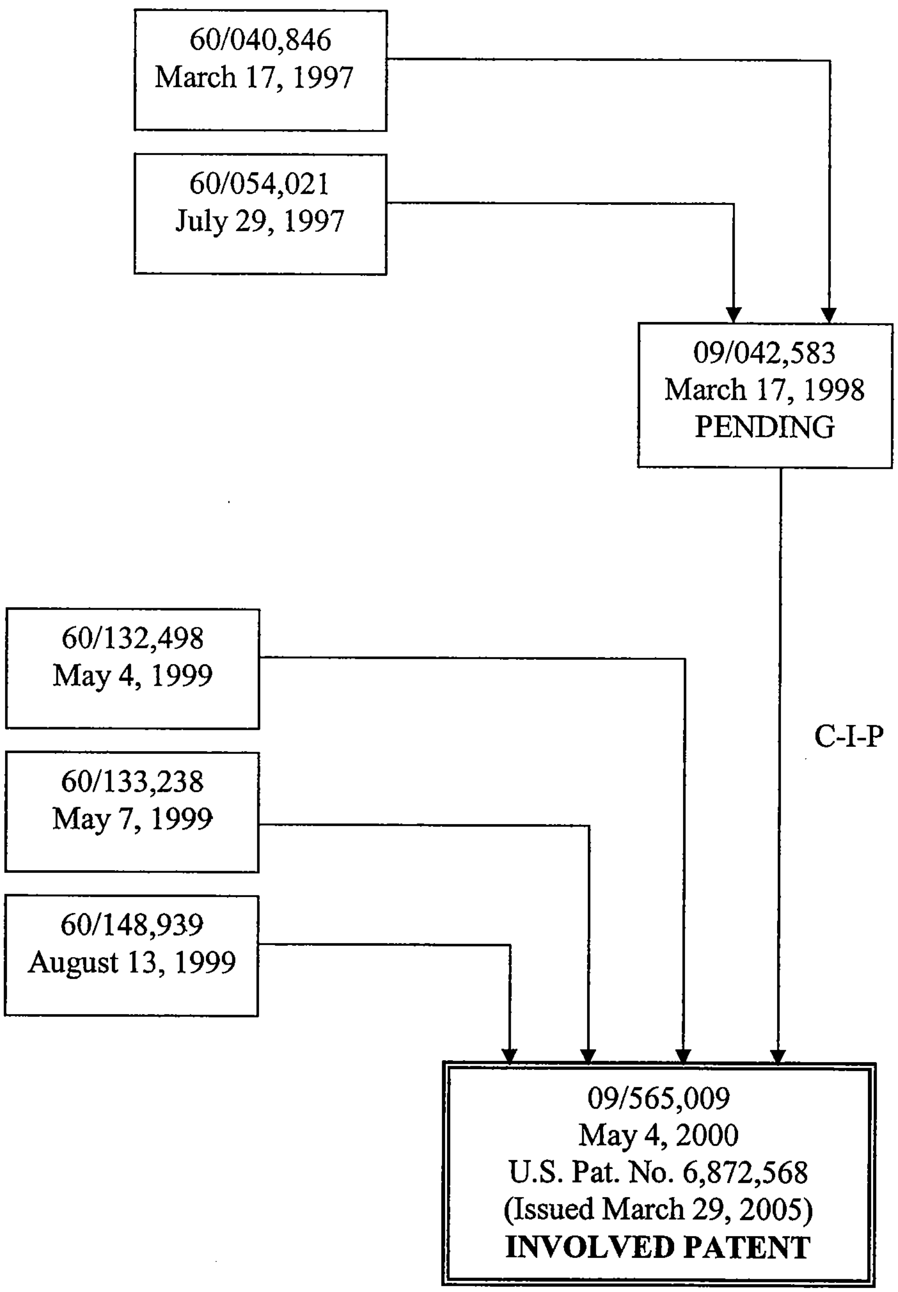
72. HGS's July 29, 1997 priority application provides a working example (Example 6) that shows that the extracellular domain of DR5 binds the cytotoxic ligand TRAIL and blocks TRAIL-induced apoptosis, and that a DR5-Fc fusion construct inhibited TRAIL-induced apoptosis. (Exhibit 2064, paragraph 54; Exhibit 2063, page 50, lines 7-38, and Figure 6B).

73. It is noted in the Declaration of Dr. John Reed that the results presented in HGS's July 29, 1997 priority application confirm the assertions from HGS's March 17, 1997 application which identified DR5 as a death receptor. (Exhibit 2064, paragraphs 54 and 55).

74. It is noted in the Declaration of Dr. John Reed that HGS's July 29, 1997 priority application provides further support for the asserted uses of agonistic and antagonistic antibodies that bind to the extracellular domain of DR5 as agents that either induce or inhibit DR5-mediated apoptosis. (Exhibit 2064, paragraph 56).

APPENDIX C TO NI SUBSTANTIVE MOTION 3
(To Change Benefit Accorded for the Contested Subject Matter)

HGS Priority Application Family Tree



APPENDIX D TO NI SUBSTANTIVE MOTION 3
(To Change Benefit Accorded for the Contested Subject Matter)

COMPARISON OF AMINO ACID NUMBERING SCHEMES FOR SEQ ID NO:2
(Original numbering of March 17, 1997 priority application on top; numbering of involved patent on bottom; ECD is highlighted)

```
                     .         .         .         .         .
  1 MEQRGQNAPAASGARKRHGPGPREARGARPGPRVPKTLVLVVAAVLLLVS   50
-51 MEQRGQNAPAASGARKRHGPGPREARGARPGPRVPKTLVLVVAAVLLLVS   -2

                     .         .         .         .         .
 51 AESALITQQDLAPQQRAAPQQKRSSPSEGLCPPGHHISEDGRDCISCKYG  100
 -1 AESALITQQDLAPQQRAAPQQKRSSPSEGLCPPGHHISEDGRDCISCKYG   49

                     .         .         .         .         .
101 QDYSTHWNDLLFCLRCTRCDSGEVELSPCTTTRNTVCQCEEGTFREEDSP  150
 50 QDYSTHWNDLLFCLRCTRCDSGEVELSPCTTTRNTVCQCEEGTFREEDSP   99

                     .         .         .         .         .
151 EMCRKCRTGCPRGMVKVGDCTPWSDIECVHKESGIIIGVTVAAVVLIVAV  200
100 EMCRKCRTGCPRGMVKVGDCTPWSDIECVHKESGIIIGVTVAAVVLIVAV  149

                     .         .         .         .         .
201 FVCKSLLWKKVLPYLKGICSGGGGDPERVDRSSQRPGAEDNVLNEIVSIL  250
150 FVCKSLLWKKVLPYLKGICSGGGGDPERVDRSSQRPGAEDNVLNEIVSIL  199

                     .         .         .         .         .
251 QPTQVPEQEMEVQEPAEPTGVNMLSPGESEHLLEPAEAERSQRRRLLVPA  300
200 QPTQVPEQEMEVQEPAEPTGVNMLSPGESEHLLEPAEAERSQRRRLLVPA  249

                     .         .         .         .         .
301 NEGDPTETLRQCFDDFADLVPFDSWEPLMRKLGLMDNEIKVAKAEAAGHR  350
250 NEGDPTETLRQCFDDFADLVPFDSWEPLMRKLGLMDNEIKVAKAEAAGHR  299

                     .         .         .         .         .
351 DTLYTMLIKWVNKTGRDASVHTLLDALETLGERLAKQKIEDHLLSSGKFM  400
300 DTLYTMLIKWVNKTGRDASVHTLLDALETLGERLAKQKIEDHLLSSGKFM  349

                     .
401 YLEGNADSAMS                                         411
350 YLEGNADSAMS                                         360
```

EXHIBIT B

Paper ______

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

(Administrative Patent Judge Richard E. Schafer)

Human Genome Sciences, Inc.
Junior Party
(Patent 6,872,568;
Inventors: Jian Ni, Reiner L. Gentz, Guo-Liang Yu, Craig A. Rosen),

v.

Genentech, Inc.
Senior Party
(Application 10/423,448;
Inventors: Camellia W. Adams, Avi J. Ashkenazi, Anan Chuntharapai, Kyung Jin Kim).

Patent Interference No. 105,361 (RES)

DECLARATION OF JOHN C. REED, M.D. PH.D.

Ni EXHIBIT 2064
Ni v. Adams
Interference No. 105,361

I, Dr. John C. Reed, hereby declare as follows:

Professional Qualifications

1. I received a Bachelor of Arts degree in Biological Chemistry from the University of Virginia in 1980, graduating Phi Beta Kappa. In 1986, I received M.D. and Ph.D. degrees from the University of Pennsylvania, School of Medicine, graduating Alpha Omega Alpha in the top 1% of my medical school class. I received my doctorate in Immunology. My thesis advisor was Dr. Peter C. Nowell, a member of the National Academy of Sciences. During my M.D., Ph.D. education, I was funded by various grants, including a grant from the National Institutes of Health (NIH) that covered my educational expenses through the Medical Scientist Training Program.

2. From 1986 to 1989, I was a Resident in Clinical Pathology at the Hospital of the University of Pennsylvania, in Philadelphia, PA. From 1986 to 1988, I was also a Postdoctoral Fellow in Molecular Biology at the Wistar Institute of Anatomy and Biology. My advisor at the Wistar Institute was Dr. Carlo Croce, a member of the National Academy of Sciences. I was the recipient of a NIH post-doctoral training grant during two of these years.

3. From 1989-1992, I was an Assistant Professor at the University of Pennsylvania School of Medicine, as well as Assistant Director of the Laboratory of Molecular Diagnosis at the Hospital of the University of Pennsylvania.

4. From 1992 to 1995, I was the Director of the Oncogene & Tumor Suppressor Program at the Burnham Institute for Medical Research (formerly the La Jolla Cancer

Research Foundation), in La Jolla, California. In 1995, I founded the Program on Apoptosis & Cell Death Research at the Burnham Institute and was Director of the program from 1995 to 2000. From 1994 to 2001, I was also the Deputy Director of the Cancer Center at the Burnham Institute, an official National Cancer Institute (NCI)-designated Cancer Center.

5. From 1995 to 2001, I was the Scientific Director of the Burnham Institute, reporting directly to the CEO & President and overseeing all scientific activities of the Burnham Institute, including setting scientific direction, recruiting faculty and other scientific staff, and managing the scientific infrastructure. In 2002, I also became the Director of the Cancer Center of the Burnham Institute, a position I held for one year, before voluntarily resigning upon recruiting a replacement director.

6. In 2002, I became the President and Chief Executive Officer of the Burnham Institute, which is the position I currently hold. The Burnham Institute for Medical Research currently employs approximately 730 persons, including more than 300 persons with advanced degrees of Ph.D. or M.D., and has an annual operating budget of over $80 million dollars.

7. Also, I am currently an Adjunct Professor in the Department of Biology at San Diego State University and an Adjunct Professor in the Department of Pathology at the University of California at San Diego, School of Medicine, a position I have held since 1997. Additionally, I am currently an Associate Member of the Whitaker Institute of Biomedical Engineering, University of California, San Diego.

8. I am the head of a research laboratory at the Burnham Institute for Medical Research. My laboratory employs approximately 40 scientists, and we are funded through research grants from various organizations, particularly the National Institutes of Health (NIH). I have been continuously funded as a principal investigator by competitive NIH grants since 1988. To date, I have been awarded 23 NIH grants for research conducted in my laboratory, and I have also received 31 additional research grants from other agencies.

9. My research focuses on the field of apoptosis and cell death regulation. My research program is broad-based, and ranges from basic discovery biology to clinical applications.

10. I have received several awards and honors from the scientific community, which are listed on my *curriculum vitae* (Exhibit 2071). Some of my recent awards include (i) the Bristol-Myers Squibb Distinguished Cancer Researcher Award (2003); (ii) the Warner-Lamber/Parke Davis Award from the Society for Investigative Pathology; (iii) the Decade's Most Highly Cited Apoptosis Researcher from 1991-2001 from the Institute for Scientific Information; (iv) the #1 Hottest Researcher in Life Sciences Worldwide (2000 and 1999) also from the Institute for Scientific Information; and recently (v) a Distinguished Graduate Award, from the University of Pennsylvania School of Medicine.

11. I have authored or co-authored over 600 publications, which are listed in my *curriculum vitae*, and I have authored or co-authored over 40 chapters in books, and have presented hundreds of abstracts at scientific meetings worldwide.

12. I am the sole inventor of a novel DNA-based therapy (Genasense^{TM}) for cancer that promotes tumor cell death by attacking an apoptosis-regulating gene. This experimental drug recently completed positive Phase III clinical trials. I have also served as scientific co-founder of biotechnology companies, based on technology from my laboratory, including IDUN Pharmaceuticals, Inc., which developed a drug that blocks apoptotic cell death and took that drug candidate successfully through Phase II clinical trials, before being acquired by Pfizer, Inc.

13. I serve or have served on the editorial boards of 31 scientific and medical journals.

14. I have been retained by counsel for Human Genome Sciences (Party Ni) to provide opinions concerning the field of apoptosis and the tumor necrosis factor (TNF) family of ligands and receptors (TNFRs), including death receptors. These topics are of considerable familiarity to me, having published at least 52 papers on the biology and biochemistry of TNF-family ligands and receptors, and nearly 500 papers on the topic of apoptosis mechanisms. In fact, according to the Institute for Scientific Information, I published more papers on the topic of apoptosis during the decade 1992-2002 than any other scientist worldwide. Thus, I feel qualified to offer opinions in this field of scientific investigation. For this work, I am compensated at the rate of $400 per hour.

15. I have reviewed (*a*) HGS's U.S. Patent Application No. 60/040,846, which appears to have been received in the U.S. Patent & Trademark Office on March 17, 1997 ("Ni's March 17, 1997 application"; Exhibit 2062); (*b*) HGS's U.S. Patent Application No. 60/054,021, which appears to have been received in the U.S. Patent & Trademark

Office on July 29, 1997 ("Ni's July 29, 1997 application"; Exhibit 2063); (*c*) HGS's U.S. Patent Application Nos. 09/042,583 (Exhibit 2073); 60/132,498 (Exhibit 2074); 60/133,238 (Exhibit 2075); and 60/148,939 (Exhibit 2076); and (*d*) HGS's involved U.S. Patent No. 6,872,568, which issued on March 29, 2005 (Exhibit 2004). Generally, the aforementioned HGS applications and patent disclose Death Receptor 5 (DR5), also known as TRAIL-Receptor-2, which is an apoptosis-inducing receptor and member of the TNF-family of death receptors. These applications and patent disclose nucleic acid and amino-acid sequences of DR5-encoding cDNAs and the predicted DR5 protein (Figure 1 of Exhibit 2062), and comment on several anticipated uses of DR5, including for production of agonistic and antagonistic monoclonal antibodies and their uses in treating diseases. The issued patent also includes data confirming that DR5 protein induces apoptosis (Figure 5 of Exhibit 2004) and binds TRAIL, a TNF-family ligand (Figure 6 of Exhibit 2004).

16. I have been informed that a "person of ordinary skill in the art" is one who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is not one who undertakes to innovate. Persons of ordinary skill could conceivably include anyone with a knowledge of the scientific literature concerning TNF-family receptors, and their ligands, that was available on or before March 17, 1997. Preferably, a "person of ordinary skill in the art" would have a scientific background such as a Bachelor's degree or higher in biological sciences, and have familiarity with techniques involved in recombinant DNA, molecular biology, and monoclonal antibody technologies.

Summary of TNF Receptors

17. TNFRs are glycoproteins that bind members of the TNF-family of cytokines and related proteins. TNFRs can be (a) transmembrane proteins, which are anchored in the plasma membrane of cells and which are comprised of an extracellular domain, transmembrane domain, and intracellular domain, or (b) they may be membrane-associated, or (c) they may be secreted proteins. By March 17, 1997, several TNFRs were known, including TNFR-1 (CD120a), TNFR-2 (CD120b), Fas (CD95), DR3 (Apo-3; TRAMP; WSL-1), CD40, CD30, and p75 NTR (low affinity receptor for Nerve Growth Factor).

18. While most TNFR-family members have been demonstrated experimentally to bind specific TNF-family ligands, some TNFR-family members do not have known ligands to date, or a delay of many years occurred before the specific ligand was established (*See, e.g.,* Locksley, RM, *et al.*, *Cell* 104: 487, (2001) (Exhibit 2077) and Ware *et al.*, *The Cytokine Handbook, Chapter 20*, pgs. 549-550 (Table 1) (1998) (Exhibit 2054)). Thus, membership in this family of receptors does not strictly require that the ligand for the receptor is known.

19. To persons of ordinary skill in the art, and as was understood in March 17, 1997, membership in the TNFR family has traditionally been based on similarity of amino-acid sequences, particularly the presence of conserved cysteine-rich domains (CRDs) located in the predicted extracellular region of the proteins, downstream of a predicted leader peptide that would target the protein either for secretion or for display on the plasma membrane, depending on whether a transmembrane domain is

also present. A canonical TNFR-family member contains, from N-terminus to C-terminus, a leader peptide, conserved cysteine-rich domain(s), a transmembrane domain, and a cytosolic domain.

20. A subset of the TNFRs also contains a conserved protein interaction module known as a Death Domain (DD) in their cytosolic domains (Tartaglia, LA *et al.*, *Cell* 74: 845 (1993) (Exhibit 2078)). Many TNFR-family members that induce apoptosis contain the Death Domain (Wallach, D. *et al.*, *TIBS* 20: 342 (1995) (Exhibit 2079)). TNFR-family members that contain DDs have been referred to as "death receptors." By March 1997, three death receptors were recognized, including TNFR1 (CD120a), Fas (APO1; CD95), and DR3 (TRAMP; WSL-1; Apo-3). Each of these receptors was known by March 17, 1997 to induce cell death by apoptosis.

21. Based on several studies conducted prior to March 17, 1997, it was known to persons of ordinary skill in the art that the apoptosis-inducing activity of death receptors is dependent on their DDs. (Tartaglia, L.A. *et al.*, *Cell* 74: 845 (1993) (Exhibit 2078); Tartaglia, L.A. & Goeddel D.V. *J Biol Chem* 267: 4304 (1992) (Exhibit 2072); Itoh *et al.*, *J. Biol. Chem.* 268: 10932 (1993) (Exhibit 2080); and Boldin, M.P. *et al.*, *J Biol Chem* 270: 387 (1995) (Exhibit 2081)). Thus, the DD is necessary and sufficient for apoptosis induction, at least when over-expressed in mammalian cells. The DD represents a modular element of TNF-family death receptors.

22. Amino acid sequence analyses of the death receptors that were known prior to March 17, 1997 indicate that such receptors shared approximately 22 to 28% sequence identity in their cysteine-rich domains and approximately 20 to 48% sequence

identity in their death domains. (Marsters *et al.*, *Current Biology* 6:1669-1676 (1996) (Exhibit 2066); Bodmer *et al.*, *Immunity* 6:79-88 (1997) (Exhibit 2067); Chinnaiyan *et al.*, *Science* 274:990-992 (1996) (Exhibit 2065)). To persons of ordinary skill in the art as of March 17, 1997, such levels of sequence identity would have been considered to be significant levels of sequence identity for death receptors.

23. By March 17, 1997, it was understood by persons of ordinary skill in the art that the activity of death receptors could be exploited for the development of therapeutics. For example, persons of ordinary skill in the art reasonably expected that agonists of death receptors, including agonistic antibodies, could be used for treating cancers due to the well known ability of TNF-family death receptors to induce apoptosis of tumor cells. Similarly, by March 17, 1997, persons of ordinary skill in the art reasonably expected that antagonists of death receptors, including antagonistic antibodies, could be used for treating various inflammatory diseases, (e.g., rheumatoid arthritis) due to the well known role of TNF-family receptors in inflammation and autoimmunity. (*See, e.g.,* Maini *et al.*, *Clin. Exp. Rheumatol.* 12 Suppl 11:S63-6 (1994) (Exhibit 2051) and Feldmann *et al.*, *Cir Shock* 43:179-84 (1994) (Exhibit 2052)).

24. By March 17, 1997, it was well known to persons of ordinary skill in the art that induction of apoptosis involves aggregation of death receptors in the cell membrane, which leads to the activation of a family of intracellular proteases ("caspases"). It was also known in March 17, 1997 that such aggregation could be caused by (i) ligand binding to the death receptor, (ii) antibody binding to the death receptor, or (iii) merely overexpressing the death receptor to cause aggregation. (*See, e.g.,* Ware *et al.*, *J. Cell Biochem.* 60:47-55 (1996) (Exhibit 2053)).

25. By March 17, 1997, the preferred method for demonstrating apoptosis-inducing activity of DD-containing TNFR-family members would have been to clone a cDNA encoding the protein into a mammalian expression plasmid and transfect that plasmid transiently into a mammalian cell line, then determine the percentage of apoptotic or dead cells relative to cells transfected with a control plasmid, usually after 1-2 days post-transfection (*See*, for example, Bodmer, J-L *et al.*, *Immunity* 6: 79 (1997) (Exhibit 2067); Chinnaiyan, AM *et al.*, *Science* 274: 990 (1996) (Exhibit 2065); Marsters, S.A. *et al., Current Biology* 6: 1669 (1996) (Exhibit 2066); and Kitson, J, *et al.*, *Nature* 384: 372, (1996) (Exhibit 2082). By March 17, 1997, it would have been routine for one of ordinary skill in the art to have carried out such an overexpression assay to test for apoptotic activity of a death receptor.

Ni's March 17, 1997 Application Discloses that DR5 is a Death Receptor

26. Ni's March 17, 1997 application (No. 60/040,846) describes a novel death receptor named DR5. As discussed below, Ni's March 17, 1997 application teaches a person of ordinary skill in the art that DR5 is a novel member of the TNF Receptor (TNFR) family of receptors (Exhibit 2062, pg. 1, lines 4-5), and that DR5 is a death domain-containing receptor (Exhibit 2062, Figure 1 and pg. 5, line 7). Ni's March 17, 1997 application describes the nucleotide and amino acid sequences of the DR5 receptor. (Exhibit 2062, Figure 1 and the DR5 cDNA clone having ATCC Deposit No. 97920).

27. By March 17, 1997, it was routine for one of ordinary skill in the art to perform sequence alignments and use computational methods for gene analysis, including the computer applications FASTDB, BLAST, MEGALIGN, CLUSTAL, and applications

found in the University of Wisconsin Genetics Computer Group (GCG) package of computer applications for gene analysis, and to use gene analysis to predict the existence of domains within novel proteins and to delineate likely functional elements of proteins (FASTDB: Brutlag *et al.*, *Comp. Appl. Biosci.* 6:237-245 (1990) (Exhibit 2083); BLAST: Altschul *et al.*, *J Mol Biol.* 215(3):403-10 (1990) (Exhibit 2084); MEGALIGN: Clewley *et al.*, *Methods Mol Biol.* 70:119-29 (1996) (Exhibit 2085); CLUSTAL: Higgins *et al.*, *Gene* 73(1):237-44 (1988) (Exhibit 2086); GCG: Devereux *et al.*, *Nucleic Acids Res.* 12(1 Pt 1):387-95 (1984) (Exhibit 2087)).

28. The deduced protein sequence of human DR5, as taught in Ni's March 17, 1997 application, has all of the features of a classical TNF-family death receptor, including (*i*) a signal (leader) peptide (amino acids 1-51 and underlined in Figure 1 of Exhibit 2062); (*ii*) an extracellular domain, including two cysteine rich domains (CRDs) (amino acids 52-184); (*iii*) a transmembrane domain (amino acids 185-208 and underlined in Figure 1 of Exhibit 2062); and (*iv*) an intracellular domain including a death domain (DD, amino acids 324-391 and italicized in Figure 1 of Exhibit 2062). (Exhibit 2062, page 5, lines 1-7). The predicted leader peptide was recognized by using the PSORT computer applications (Nakai and Kanehisa, *Genomics* 14:897-911, 1992 (Exhibit 2088)), which was a technique well known to those of ordinary skill in 1997.

29. Ni's March 17, 1997 application describes the regions of similarity between the amino acid sequences of DR5 and the death receptors known as of March 17, 1997: human TNFR1, human Fas, and the death domain-containing receptor 3 (DR3) (Exhibit 2062, Figure 2). Ni's March 17, 1997 application discloses that, of the then-known

members of the TNF family of receptors, DR5 shares the highest degree of homology with human TNFR1, Fas and DR3 (Exhibit 2062, page 6, lines 28-30).

30. Each of the cysteine rich domains (CRD) of DR5 shares significant (approximately 22-35%) amino-acid sequence identity with CRDs found in the then-known death receptors Fas, TNFR1, and DR3. To one of ordinary skill in the art, this degree of sequence identity would be recognized as significant, and was of comparable similarity to other well-known death receptors. For example, the CRD of the TRAIL-R2 sequence described by Ni, *et al.*, shares: 22.4 % homology to Fas/CD95; 30% homology to TNFR1a; and 34.5% homology to DR3, based on an analysis undertaken using Lipman-Pearson Protein Alignment (with the following parameters: Ktuple 2; Gap Penalty 4; Gap Length Penalty 12). By comparison, Chinnaiyan *et al.* reported that "the identity of the cysteine-rich subdomains of the clone [DR3] with those of TNFR-1 and CD95 was 26% and 22%, respectively, consistent with the 20 to 30% identity reported for the known TNFR family members." (Chinnaiyan *et al.*, *Science* 274: 990-992 (1996) (Exhibit 2065)). In addition, Marsters *et al.* reported that the extracellular domain of DR3 shares: 28% homology to TNFR1 and 25% homology to CD95." (Marsters *et al.*, *Current Biology* 6:1669-1676 (1996) (Exhibit 2066)). Also, Bodmer *et al.* reported that the CRD of DR3 (Tramp) shares: 29% homology to TNFR1 and 24% homology to CD95, while TNFR1 and CD95 share 22% homology in their CRD." (Bodmer J-L *et al.*, *Immunity* 6:79-88 (Jan. 1997) (Exhibit 2067)). Thus, the CRDs of TRAIL-R2 (DR5) described by Ni are readily recognizable to one of ordinary skill in the art as being significantly similar to the CRDs of other well-known death receptors.

31. The death domain (DD) of the deduced DR5 protein described in Ni's March 17, 1997 application also shares significant (approximately 21-33%) amino-acid sequence identity with the DDs of the then-known death receptors Fas, TNFR1, and DR3. To one skilled in the art, this degree of sequence identity would be recognized as significant, and was of comparable similarity to other well-known death receptors. For example, the death domain of TRAIL-R2 reported by Ni shares: 21.1% to Fas/CD95; 32.1% to TNFR1a; and 32.8% to DR3, based on an analysis undertaken using Lipman-Pearson Protein Alignment (with the following parameters: Ktuple 2; Gap Penalty 4; Gap Length Penalty 12). By comparison, Chinnaiyan *et al.* reported that "The clone [DR3] contained significant homology to the death domains of TNFR-1 (47% identity) and CD95 (23% identity)." (Chinnaiyan *et al.*, *Science* 274: 990-992 (1996) (Exhibit 2065)). In addition, Marsters *et al.* reported that "the death domain of DR3 shares: 48% homology to TNFR1 and 20% homology to CD95." (Marsters *et al.*, *Current Biology* 6:1669-1676 (1996) (Exhibit 2066)).

32. In view of the disclosure in Ni's March 17, 1997 application, including the similarity of DR5 to previously-known death receptors (TNFR1, Fas and DR3, each of which was known to induce apoptosis), and in view of the state of the art prior to March 17, 1997, the most reasonable conclusion to draw from Ni's March 17, 1997 application is that DR5 is expected, by persons of ordinary skill in the art, to be a novel death receptor. Additionally, in view of Ni's March 17, 1997 application and the state of the art, a person of ordinary skill in the art would have predicted that activation of DR5 would induce apoptosis. Such a conclusion is explicitly stated in Ni's March 17, 1997 application (Exhibit 2062, page 6, lines 25-33), and, based on the information

provided in Ni's March 17, 1997 application and what was known at the time, a person of ordinary skill in the art would have reasonably believed this assertion.

Ni's March 17, 1997 Application Describes Methods for Making and Using Agonist and Antagonist Antibodies that Bind to the Extracellular Domain of DR5

33. Ni's March 17, 1997 application describes methods for making agonist and antagonist antibodies that bind to the extracellular domain (ECD) of DR5. To make and use such antibodies, one of ordinary skill in the art would typically (1) produce monoclonal antibodies that specifically bind to the ECD of DR5 and (2) determine by routine screening whether the monoclonal antibodies are agonists or antagonists of DR5.

34. By March 17, 1997, the information disclosed in Ni's March 17, 1997 application would have been sufficient for one of ordinary skill in the art to produce antibodies that specifically bind to the ECD of DR5, using methods well known to persons of ordinary skill in the art. As discussed below, it would not have required an undue amount of experimentation by March 17, 1997 for a person of ordinary skill in the art to produce, identify, and use agonistic and antagonistic monoclonal antibodies that bind to the ECD of DR5.

35. I have been informed that certain factors should be considered in determining whether a given amount of experimentation would constitute "undue experimentation." In concluding that such experimentation would not have been undue, I have therefore considered, among other things:

a. The nature of the invention, which is monoclonal antibodies; monoclonal antibody technology was well-known to persons of ordinary skill in the art by March 17, 1997;

b. The state of the art as it existed by March 17, 1997, which included demonstrations by others that agonistic and antagonistic antibodies could be made that bind to the death receptors Fas and TNFR1, proteins highly similar to DR5 (Itoh, N. *et al.*, *Cell* 66: 233 (1991) (Exhibit 2089); Yonehara, S *et al.*, *J. Exp. Med.* 169: 1747 (1989) (Exhibit 2090); Trauth, B.C. *et al.*, *Science* 245: 301 (1989) (Exhibit 2091); Cifone, MG *et al.*, *J. Exp. Med.* 177: 1547 (1993) (Exhibit 2092); Tartaglia, L.A. *et al.*, *Proc. Natl. Acad. Sci.* 88: 9292 (1991) (Exhibit 2093); Tartaglia L.A. & Goeddel D.V., *J. Biol. Chem.* 267: 4304 (1992) (Exhibit 2072); Espevik T. *et al.*, *J. Exp. Med.* 171: 415 (1990) (Exhibit 2095); Engelmann, H. *et al.*, *J. Biol. Chem.* 265: 14497 (1990) (Exhibit 2096); Sheehan, K.C.F. *et al.*, *J. Exp. Med.* 181: 607 (1995) (Exhibit 2097); Fadeel, B. *et al.*, *International Immunol.* 9: 201 (1997) (Exhibit 2098); Alderson, M.R. *et al.*, *International Immunol.* 6: 1799 (1994) (Exhibit 2099).

c. The level of one of ordinary skill, which is high since, as discussed above, such a person would have had a knowledge of the scientific literature concerning TNFRs, and more particularly the death receptors, and their ligands, preferably a Bachelor's degree or higher in the biological sciences, and would have a general familiarity with techniques involved in recombinant DNA, molecular biology, and monoclonal antibody techniques.

d. The level of predictability in the field, which is high since one would have had a substantial degree of confidence in being able to produce agonistic and antagonistic antibodies that bind to a death receptor such as DR5;

e. The amount of direction provided by the inventors in the March 17, 1997 application, which is substantial, since the application discloses the complete nucleotide and deduced amino acid sequences of DR5 and it indicates the location of the extracellular domain and death domain of DR5, and also discloses the similarity of DR5 to other death receptors;

f. The existence of working examples (*i.e.*, experiments that were actually carried out) in the March 17, 1997 application; although the March 17, 1997 application does not exemplify experiments that were actually carried out on agonistic and antagonistic antibodies, the absence of such examples would not prevent persons of ordinary skill in the art from obtaining and using such antibodies; and

g. The quantity of experimentation needed, based on the content of the March 17, 1997 application, to make or use agonistic and antagonistic antibodies that bind to DR5; although a person of ordinary skill in the art would need to screen a number of antibodies to identify agonistic and antagonistic monoclonal antibodies that bind to the ECD of DR5, such screening would have been routine for a person of ordinary skill in the art by March 17, 1997. Additionally, persons of ordinary skill in the art would have been prepared to screen a considerable number of antibodies to identify agonistic and antagonistic monoclonal

antibodies that bind to the ECD of DR5, and such a person would have been able to distinguish such agonistic antibodies from antagonistic antibodies.

36. As discussed above, Ni's March 17, 1997 application describes the DR5 nucleotide and deduced amino acid sequence, including the amino acid sequence of the ECD. Ni's March 17, 1997 application describes the cDNA sequence encoding the predicted DR5 protein as shown in Figure 1 (Exhibit 2062). The DR5 cDNA could have been employed to express in bacteria the mature extracellular domain of DR5, corresponding to amino-acid residues 52-184, as shown in Figure 1 of Ni's March 17, 1997 application (Exhibit 2062). Ni's March 17, 1997 application also describes the deposited DR5 cDNA clone (ATCC No. 97920), which could have been used by one of ordinary skill in the art to produce a DR5 polypeptide in order to produce antibodies that bind to DR5. (Exhibit 2062, pg. 3, lines 22-25).

37. Based on the description in Ni's March 17, 1997 application, and knowledge in the art by March 17, 1997, expression of the extracellular domain of DR5 for the purposes of creating a purified protein for antibody production would have been routine to one of ordinary skill in the art. Methods for engineering expression plasmids for the purpose of producing recombinant proteins in bacteria were well established by March 17, 1997, including use of the Polymerase Chain Reaction (PCR) with specific synthetic DNA primers to amplify only the region of the cDNA that one wishes to express, and methods for cloning PCR products into bacterial expression plasmids. The methods for engineering expression plasmids for the purpose of producing recombinant proteins in bacteria were well established by March 17, 1997. (*See, e.g.*, Exhibit 2062, Example 1, pgs. 34-35).

38. Using techniques that were routine by March 17, 1997, one of ordinary skill in the art could have purified the expressed DR5 polypeptide (or a fragment thereof). For example, the mature extracellular domain of DR5, corresponding to residues 52-184, could have been produced as a fusion protein with a variety of affinity tags that aid subsequent purification of the expressed proteins, such as the hexa-histidine tag (His6) for purification using Ni-chelation resin, the glutathione-sulfo-transferase (GST) tag, for affinity purification using immobilized glutathione, and others. Additionally, one of ordinary skill in the art could have used routine techniques to produce fusion proteins (*e.g.*, IgG constant domain fusions) to facilitate purification of DR5 (or a fragment of DR5). (Exhibit 2062, pg. 25, lines 3-14). Accordingly, such methods could have been carried out by a person of ordinary skill in the art without undue experimentation by March 17, 1997.

39. By March 17, 1997, it would have been routine for a person of ordinary skill in the art to immunize animals (*e.g.*, mice, rats, rabbits or other species) with a purified protein, such as purified DR5. Polyclonal antibodies then could have been obtained from the animals' serum without undue experimentation. (Exhibit 2062, *e.g.*, Examples 1-3 at pgs. 34-42). For example, one of ordinary skill in the art would have used the extracellular domain of the DR5 receptor (or a portion of the extracellular domain) to raise antibodies that were reactive against portions of the DR5 receptor exposed on the surface of a cell. Thus, by March 17, 1997, in view of the disclosure in Ni's March 17, 1997 application, a person of ordinary skill in the art could have readily made polyclonal antibodies that bind to DR5.

40. Alternatively, particularly for mice, splenocytes could be isolated from immunized animals and fused with myeloma cells to create hybridomas that produce monoclonal antibodies. Such techniques were well known by March 17, 1997, and a person of ordinary skill in the art could have, without undue experimentation, used such techniques to produce monoclonal antibodies that bind to the ECD of DR5. (*See, e.g.*, Kohler and Milstein, *Nature* 256(5517):495-7(1975)) (Exhibit 2094). Thus, in view of the disclosure in Ni's March 17, 1997 application, together with what was already known, a person of ordinary skill in the art could have produced monoclonal antibodies that bind to the ECD of DR5 without undue experimentation.

41. Additional options for antibody production also existed by March 17, 1997. In addition to using bacteria-expressed recombinant proteins for immunization, several other methods for producing antibodies to transmembrane receptors were known by March 17, 1997. These methods include, but are not limited to: (a) expressing the receptor proteins on the surface of cells and immunizing animals with those cells, which is a method that was used to produce anti-Fas antibodies in 1993 (Cifone, MG *et al.*, *J Exp Med* 177: 1547 (1993)(Exhibit 2092)); (b) expressing the receptor protein or fragments of it using alternatives to bacterial expression systems, including yeast, insect, and mammalian expression systems, purifying the expressed protein for use as an immunogen; (c) synthetically synthesizing peptides corresponding to portions of the receptor, preferably the extracellular domain, covalently linking those peptides to immunogenic carrier proteins such as Keyhole Limpets Hemocyanin (KLH) or chicken ovalbumin (OVA), and using the peptide conjugates as immunogens. Thus, in view of the disclosure in Ni's March 17, 1997 application, it would have been

routine for one of ordinary skill in the art by March 17, 1997 to produce antibodies that bind to the ECD of DR5, as discussed above.

42. By March 17, 1997, and in view of the disclosure in Ni's March 17, 1997 application, one of ordinary skill in the art also would have been able to identify agonist and antagonist antibodies that specifically bind to the ECD of DR5, without undue experimentation. Specifically, a person of ordinary skill in the art would have needed to determine whether a particular monoclonal antibody that specifically binds to the extracellular domain of DR5 either (a) enhanced or potentiated apoptosis (agonists) or (b) inhibited apoptosis (antagonists).

43. Ni's March 17, 1997 application provides a method for assaying for DR5-induced apoptosis and cites several scientific references that illustrate the method (Exhibit 2062, pg. 43, line 11, through pg. 44, line 4). As summarized in this example, DR5 is expressed in MCF7 human breast carcinoma cells and 293 human embryonic kidney cells, and the morphological characteristics of the cells are observed. Cells in which apoptosis is induced by DR5 expression become rounded and condensed and detach from the culture dish. By March 17, 1997, a person of ordinary skill in the art would have understood that the apoptosis assay of this Example could have been conducted in the presence or absence of an antibody. If the addition of the antibody resulted in an increase in the extent of apoptosis as compared to the extent of apoptosis observed in a control experiment lacking the antibody, then a person of ordinary skill in the art would have characterized the antibody an agonist of DR5. Conversely, if the addition of the antibody resulted in a decrease in the extent of apoptosis as compared to the extent of apoptosis observed in a control experiment lacking the antibody, then a

person of ordinary skill in the art would have characterized the antibody as an antagonist of DR5. Conducting such screening experiments as of March 17, 1997 would not have required undue experimentation.

44. Ni's March 17, 1997 application describes several additional assays to screen for an antibody that is an agonist or antagonist of a death receptor, for example, at page 27, line 25, through page 29, line 6. Included in the application is a citation to Tartaglia and Goeddel, *J. Biol. Chem.* 267: 4304-4307 (1992) (Exhibit 2072), which describes an assay of the induction of cell death by antibodies that bind to TNF-R1.

45. Thus, based on what was known by March 17, 1997 and what was disclosed in Ni's March 17, 1997 application, it would not have required undue experimentation for a person of ordinary skill in the art to screen for agonist antibodies that bind to the ECD of DR5; similarly, it would not have required undue experimentation for a person of ordinary skill in the art to screen for antagonist antibodies that bind to the ECD of DR5.

46. As discussed below, Ni's March 17, 1997 application also discloses how to use such antibodies in, *e.g.*, therapeutic or diagnostic applications. In view of the disclosure in the March 17, 1997 application and in view of what was known as of March 17, 1997, a person of ordinary skill in the art would not have had to resort to undue experimentation to be able to use agonist or antagonist antibodies that bind to the ECD of DR5.

Ni's March 17, 1997 Application Describes Reasonable Methods for Producing Agonist and Antagonist Antibodies that Bind to the ECD of DR5 and it Provides a Clear Description of Such Antibodies

47. Upon reviewing Ni's March 17, 1997 application, a person of ordinary skill in the art would have understood that the application included reasonable methods for producing monoclonal antibodies that specifically bind to the extracellular domain of DR5 and which are agonists or antagonists of DR5. Such methods are clearly disclosed in the March 17, 1997 application by virtue of, among other things, a description of the ECD of DR5, which can be used as an antigen to make such antibodies. The ECD of DR5 is disclosed in detail in the March 17, 1997 application, as its complete amino acid sequence is provided. Additionally, the March 17, 1997 application discloses methods for producing agonist and antagonist monoclonal antibodies using such an antigen without resorting to undue experimentation. Thus, Ni's March 17, 1997 application conveys that the inventors disclosed methods for producing agonist and antagonist antibodies that bind specifically to the ECD of DR5.

48. Additionally, I have been informed that a patent application is not required to include a demonstration that an invention has actually been made in order for the application to include an adequate description of such an invention. Ni's March 17, 1997 application provides a clear description of polyclonal antibodies and agonist and antagonist monoclonal antibodies that bind to the ECD of DR5. For example, by providing the amino acid sequence of the ECD of DR5, along with methods for producing and screening agonist and antagonist antibodies, Ni's March 17, 1997 application clearly sets forth the applicants' invention. Indeed, Ni's application provides sufficient detail regarding such agonist and antagonist antibodies that a

person of ordinary skill in the art could distinguish such antibodies from other agonist and antagonist monoclonal antibodies. Accordingly, Ni's March 17, 1997 application clearly conveys to a person of ordinary skill in the art that the inventors had described monoclonal agonist and antagonist antibodies that specifically bind to the ECD of DR5, and that the inventors recognized that they had described such antibodies. Similarly, Ni's March 17, 1997 application clearly conveys to a person of ordinary skill in the art that the inventors had described polyclonal antibodies that bind to the ECD of DR5.

49. Based on precedent from prior work in the field of TNF-family receptors, it would have been reasonable, by March 17, 1997, to believe that antibodies directed against the DR5 protein would be capable of either inducing or blocking apoptosis. For example, it had been shown that some monoclonal antibodies directed against Fas (CD95; APO1), a death receptor that shares substantial sequence similarity with DR5 in all critical predicted domains outlined above, function as agonists, mimicking the effects of ligand, and inducing apoptosis of cells that express Fas on their surface (Itoh, N. *et al., Cell* 66: 233 (1991) (Exhibit 2089); Yonehara, S. *et al., J. Exp. Med.* 169: 1747 (1989) (Exhibit 2090); Trauth, B.C. *et al., Science* 245: 301 (1989) (Exhibit 2091); Cifone, MG *et al., J. Exp. Med.* 177: 1547 (1993) (Exhibit 2092)). Similar agonistic antibodies had also been produced to TNFR1 by March 1997, and shown to induce cell death, thus mimicking the ligand TNF (Tartaglia, L.A. *et al., Proc. Natl. Acad. Sci.* 88: 9292 (1991) (Exhibit 2093); Tartaglia L.A. & Goeddel D.V., *J. Biol. Chem.* 267: 4304 (1992)(Exhibit 2072); Espevik T. *et al., J. Exp. Med.* 171: 415 (1990) (Exhibit 2095); Engelmann, H. *et al., J. Biol. Chem.* 265: 14497

(1990) (Exhibit 2096)). TNFR1 also shares substantial sequence similarity with the DR5 protein described in Ni's March 17, 1997 application, as outlined above. Alternatively, some antibodies directed against Fas or TNFR1 were known to neutralize (antagonize) the activities of these receptors (Sheehan, K.C.F. *et al., J. Exp. Med.* 181: 607 (1995) (Exhibit 2097); Fadeel, B. *et al., International Immunol.* 9: 201 (1997) (Exhibit 2098)), or in some cases to reveal additional activities of the receptors, such as stimulating proliferation of immune cells (Alderson, M.R. *et al., International Immunol.* 6: 1799 (1994) (Exhibit 2099)). Thus, prior to March 17, 1997 agonist and antagonist antibodies had been identified for other death receptors.

50. Based on precedent from the literature where agonistic and antagonistic antibodies to other TNF-family death receptors had been produced and characterized, and based on the information provided in Ni's March 17, 1997 application it would have been reasonable for one of ordinary skill in the art to believe that agonistic antibodies that specifically bind to DR5 would induce apoptosis of tumor cells and that antagonistic antibodies that specifically bind to DR5 would suppress apoptosis. To confirm this belief experimentally, a person of ordinary skill in the art would have simply needed to determine whether a particular monoclonal antibody that specifically binds to the extracellular domain of DR5, either (a) enhanced apoptosis (agonists) or (b) inhibited apoptosis (antagonists).

51. Ni's March 17, 1997 application describes therapeutic uses for agonist and antagonist antibodies against DR5. (Exhibit 2062, pg. 26, line 27, though pg. 27, line 17; pg. 35, lines 12-24). For example, the application discloses that agonistic antibodies can be used in methods for treating cancers by enhancing apoptosis. (Exhibit 2062, pg. 32,

lines 20-21). Additionally, the application discloses that antagonist antibodies can be used in methods for treating inflammatory diseases, such as rheumatoid arthritis and HIV. (Exhibit 2062, pg. 32, lines 17-19 and pg. 31, lines 10-37). Such uses would have been believable to one of ordinary skill in the art reading Ni's March 17, 1997 application in view of what was known of the value of therapeutic agonistic or antagonistic antibodies that bind to apoptosis-inducing molecules.

52. Ni's March 17, 1997 application also describes diagnostic uses for antibodies to DR5, *e.g.*, in assays for detecting levels of DR5 protein in cells and tissues, including the determination of normal and abnormal levels. (Exhibit 2062, pg. 25, line 16, through pg. 26, line 2). Such uses would have been believable to one of ordinary skill in the art reading Ni's March 17, 1997 application.

Ni's July 29, 1997 Application Describes How to Make and Use Agonistic and Antagonistic Antibodies that Bind to DR5

53. My statements and opinions set forth in paragraphs 1 through 52, above, also apply to Ni's July 29, 1997 application (Application No. 60/054,021; Exhibit 2063).

54. Ni's July 29, 1997 application supplements the disclosure in Ni's March 17, 1997 application and also contains data that confirm various assertions made in the March 17, 1997 application. For example, Ni's July 29, 1997 application discloses that the protein expressed from the cDNA that contains the open reading frame (ORF) of the predicted human DR5 protein behaves similar to other known TNF-family death receptors, in that: (a) DR5 induces cell death upon over-expression in mammalian cells (Exhibit 2063; Figure 5); (b) the cell death is dependent on the presence of the DD in DR5 (Exhibit 2063; Figures 5A, B); (c) the DR5-induced cell death is

suppressed by known caspase-inhibitors (*e.g.*, CrmA protein and the compound zVAD-fmk) (Exhibit 2063; Figures 5C, E); and (d) apoptosis induced by DR5 is suppressed by expression of a dominant-negative mutant of the caspase-family member FLICE2 (caspase-10) (Exhibit 2063; Figure 5E).

55. Ni's July 29, 1997 application also presents evidence that the DR5 protein can bind TRAIL, based on experiments where the extracellular domain of DR5 was expressed as a fusion protein with the Fc region of IgG, and this DR5-Fc fusion protein was used to bind FLAG-epitope tagged TRAIL (Exhibit 2063; Figure 6A) and used to neutralize TRAIL (but not TNF) with respect to induction of apoptosis of tumor cells (Exhibit 2063; Figures 6B, C). The results presented in Ni's July 29, 1997 application thus confirm the assertions in Ni's March 17, 1997 application that DR5 is a death receptor.

56. Ni's July 29, 1997 application thus provides further support for the asserted uses of agonist and antagonist antibodies that bind to the extracellular domain of DR5 as agents that either induce or inhibit DR5-mediated apoptosis.

57. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent.

12-7-05
Date

John C. Reed, M.D., Ph.D.

EXHIBIT C

Paper No. _______

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Richard E. Schafer)

Human Genome Sciences, Inc.
Junior Party
(Patent 6,872,568;
Inventors: Jian Ni, Reiner L. Gentz, Guo-Liang Yu, Craig A. Rosen),

v.

Genentech, Inc.
Senior Party
(Application 10/423,448;
Inventors: Camellia W. Adams, Avi J. Ashkenazi, Anan Chuntharapai, Kyung Jin Kim).

Patent Interference No. 105,361 (RES)

ADAMS OPPOSITION 3
(Opposing Ni Substantive Motion 3)

Appendix A

THE EVIDENCE

I. Exhibits Cited

The following exhibits are cited in support of this opposition:

AX-1036 U.S. Patent Application No. 60/054,021 to Ni *et al.*, filed on 7/29/97.

AX-1037 U.S. Patent Application No. 60/040,846 to Ni *et al.*, filed on 3/17/97

AX-1040 U.S. Patent Application No. 60/046,615, filed on 5/15/97.

AX-1046 Liu *et al.*, *Cell* 87:565-576 (1996).

AX-1048 Edelman, *Antibody Structure and Molecular Immunology*, Nobel Lecture (December 12, 1972)

AX-1049 Yelton & Scharff, *American Scientist* 68:510-516 (1980).

AX-1050 Sevier *et al.*, *Clinical Chemistry* 27:1797-1806 (1981).

AX-1053 Curtiss and Witzum, *J. Clin. Invest.* 72(4):1427-1438 (1983).

AX-1054 Kehoe & Seide, *J. Am. Vet. Med. Assoc.* 181(10):1000-1004 (1982).

AX-1055 Kabat *et al.*, *Proc. Nat. Acad. Sci.* 73:4471-4473 (1976).

AX-1056 Novotny *et al.*, *J. Biol. Chem.* 258:14433-14437 (1983)

AX-1058 Gruss *et al.*, *Blood* 85:3378-3404 (1995).

AX-1059 DeBenedette *et al.*, *J. Exp. Med.* 181:985-992 (1995).

AX-1060 Mapara *et al.*, *Eur. J. Immunol.* 23:702-708 (1993).

AX-1064 Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, pp. 29-30, Ninth Edition (1996).

AX-1065	Nagata, *Cell* 88:355-365 (1997).
AX-1066	Eischen *et al.*, *Blood* 90:935-943 (August 1997).
AX-1068	Rabizadeh *et al.*, *Science* 261:345-348 (1993).
AX-1069	Chapman *et al.*, *FEBS Letters* 374:216-220 (1995).
AX-1070	Beg *et al.*, *Science* 274:782-784 (1996).
AX-1071	Van Antwerp *et al.*, *Science* 274:787-789 (1996).
AX-1072	Wang *et al.*, *Science* 274:784-787 (1996).
AX-1073	WO 92/01810 to Lerner *et al.*, published on 02.06.92.
AX-1074	Chu, *J. Bio. Chem.* 269(2):787-790 (1994).
AX-1075	Prakash and Timasheff, *J. Bio Chem.* 258(3):1689-1697 (1983).
AX-1076	Feinstein *et al.*, *TIBS* 20:342-344 (1995).
AX-1077	Hofmann *et al.*, *FEBS Letters* 371:321-323 (1995).
AX-1078	Alderson *et al.*, *J. Exp. Med.* 178:2231-2235 (1993).
AX-1079	Chinnaiyan *et al.*, *Cell* 81:505-512 (1995).
AX-1080	Hess *et al.*, *J. Exp. Med.* 183:159-167 (1996).
AX-1081	Sato *et al.*, *FEBS Letters* 358:113-118 (1995).
AX-1082	Liu *et al.*, *Nature* 342:929-931 (1989).
AX-1083	Tsubata, *Nature* 364:645-648 (1993).
AX-1084	Hsu *et al.*, *Cell* 81:495-504 (1995).

AX-1085	Brojatsch *et al.*, *Cell* 87: 845-855 (1996).
AX-1086	Declaration of Dr. Michael Karin.
AX-1092	Reed, *American Journal of Pathology* 157(5):1415-1430 (2000).
AX-1095	Doctor *et al.*, *Cell Death and Differentiation* 10:621-633 (2003).
AX-1096	Reed *et al.*, *Sci. STKE* 2004, re9 (2004).
NX-2004	USP No. 6,872,568 to Ni et al, issued on 3/29/06.
NX-2021	Sheridan *et al.*, *Science* 277:818-821 (1997).
NX-2022	Pan *et al.*, *Science* 277:815-818 (1997).
NX-2053	Ware, *J. Cell. Biochem.* 60:47-55 (1996).
NX-2064	Declaration of John C. Reed, MD, PhD.
NX-2065	Chinnaiyan *et al.*, *Science* 274:990-992 (1996).
NX-2066	Marsters *et al.*, *Current Biology* 6(12):1669-1676 (1996).
NX-2072	Tartaglia *et al.*, *J. Biol. Chem.* 267:4304-4307 (1992).
NX-2078	Tartaglia *et al.*, *Cell* 74:845-853 (1993).

II. Papers Cited

The following papers are cited in support of this opposition:

Paper No. 1	Notice Declaring Interference, filed on August 31, 2005.
Paper No. __	Ni Substantive Motion 4, filed on December 7, 2005.

III. Appendices Cited

The following appendices are cited in support of this opposition:

Appendix A	The Evidence.
Appendix B	Statement of Material Facts Relied Upon in Opposition.

Appendix B

STATEMENT OF MATERIAL FACTS RELIED UPON IN OPPOSITION

I. Counts 1 and 2 and Proposed Counts 3 and 4

75. Count 1 is defined as "An **isolated monoclonal antibody** or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2 wherein said antibody or fragment thereof is an antagonist of the protein of SEQ ID NO:2." (AX-1086, ¶ 33; NX-2004; and Paper No. 1, filed on August 31, 2005; Emphasis added).

76. Count 2 is defined as "An **isolated monoclonal antibody** or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2 wherein said antibody or fragment thereof is an agonist of the protein of SEQ ID NO:2." (AX-1086, ¶ 34; NX-2004; and Paper No. 1, filed on August 31, 2005; Emphasis added).

77. Proposed Count 3 is defined as "An **isolated antibody** or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2 wherein said antibody or fragment thereof is an antagonist of the protein of SEQ ID NO:2." (AX-1086, ¶ 35 and Ni Substantive Motion 4, filed on December 7, 2005; Emphasis added).

78. Proposed Count 3 is the same as Count 1, except Count 1 states the term "monoclonal" and Proposed Count 3 does not state the term "monoclonal." (AX-1086, ¶ 36).

79. Proposed Count 4 is defined as "An **isolated antibody** or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2 wherein said antibody or fragment thereof is an agonist of the protein of SEQ ID NO:2." (AX-1086, ¶ 37 and Ni Substantive Motion 4, filed on December 7, 2005; Emphasis added).

80. Proposed Count 4 is the same as Count 2, except Count 2 states the term

"monoclonal" and Proposed Count 4 does not state the term "monoclonal." (AX-1086, ¶ 38).

II. Adams's and Ni's Applications

81. Adams filed Provisional Application No. 60/046,615 ("the '615 application") on May 15, 1997. (AX-1040).

82. Ni filed Provisional Application No. 60/040,846 ("the '846 application") on March 17, 1997. (AX-1037).

83. Ni filed Provisional Application No. 60/054,021 ("the '021 application") on July 29, 1997. (AX-1036).

III. Level of Skill Possessed by a Person of Ordinary Skill in the Art

84. A person of ordinary skill in the field of TNF receptor research as of March 17, 1997 and as of July 29, 1997, would have been an individual who (i) had an advanced degree in molecular biology, cell biology, biochemistry or similar discipline or had significant laboratory experience and knowledge of the literature in the field, (ii) was familiar with techniques for production of monoclonal antibodies and (iii) had experience in characterization and assessment of TNFR family members. (AX-1086, ¶ 39).

IV. Antibody Technology as of March 17, 1997

A. Antibody Overview

85. An antibody is a protein that selectively binds to a specific location on an antigen (termed an "epitope"). (AX-1086, ¶ 41).

86. The general structure of an antibody molecule was well known prior to March 17, 1997. (AX-1086, ¶ 42 and AX-1048, Fig. 3).

87. An antibody generally contains two pairs of polypeptides. (AX-1086, ¶ 42 and AX-1048, Fig. 3).

88. Each pair of polypeptides contains one "heavy" polypeptide chain and one "light" polypeptide chain. (AX-1086, ¶ 42 and AX-1048, Fig. 3).

89. Each of the polypeptide chains contains "constant" and "variable" domains. (AX-1086, ¶ 42 and AX-1048, Fig. 3).

90. A representative diagram of an antibody of the IgG isotype is shown below. *See*, Figure 3 of *Antibody Structure and Molecular Immunology*, Nobel Lecture, December 12, 1972, by Gerald M. Edelman. The variable regions are shaded, while the constant regions are unshaded. (AX-1086, ¶ 42 and AX-1048, Fig. 3).

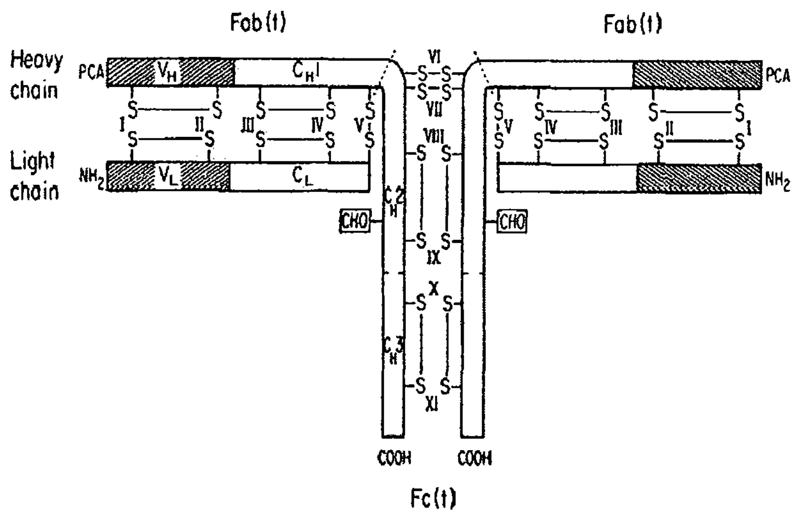

Fig. 3.
Overall arrangement of chains and disulfide bonds of the human γG_1 immunoglobulin *Eu*. Half-cystinyl residues are I-XI; I-V designates corresponding half-cystinyl residues in light and heavy chains. PCA, pyrrolidonecarboxylic acid; CHO, carbohydrate. Fab(t) and Fc(t) refer to fragments produced by trypsin, which cleaves the heavy chain as indicated by dashed lines above half-cystinyl residues VI. Variable regions, VH and VL, are homologous. The constant region of the heavy chain (CH) is divided into three regions, CH1, CH2 and CH3, that are homologous to each other and to the C region of the light chain. The variable regions carry out antigen-binding functions and the constant regions the effector functions of the molecule.

91. The constant domains of an antibody have a generally consistent and conserved structure within each isotype (*e.g.*, IgG) of antibody in a mammal, and play a role in certain

immune system modulating functions (*e.g.*, complement fixation), but typically do not play a role in antigen binding. (AX-1086, ¶ 43 and AX-1049, p. 510, col. 3, last ¶).

92. The variable domains are amino acid sequences within the light and heavy polypeptide chains, which vary between antibody molecules with different binding specificities. (AX-1086, ¶ 44 and AX-1049, p. 510, col. 3, ¶ 2).

93. The ability of an antibody to bind to a specific epitope is attributable to the structure defined by the variable domains of the antibody. (AX-1086, ¶ 44 and AX-1049, p. 510, col. 3, ¶ 2).

94. Multiple antibodies can bind to one antigen yet exhibit distinct binding specificities and cause distinct biological effects, as each antibody may bind to a distinct epitope on the antigen. (AX-1086, ¶ 45 and AX-1050, p. 1798, col. 1, ¶¶ 2 and 3).

B. <u>Observations on Antibody Issues of Relevance to the Interference</u>

95. Each antibody molecule in a monoclonal antibody molecule composition will bind to the same epitope on the antigen used to produce the antibody. (AX-1086, ¶ 51 and AX-1050, p. 1798, col. 1, ¶ 2, last sentence).

96. Where the antigen is a cell surface receptor protein, such as a DR5, the epitope to which any particular antibody binds often will not correspond to a linear sequence of amino acids found in the polypeptide. (AX-1086, ¶ 51 and AX-1053, Abstract and p. 1435, col. 1, ¶ 2).

97. As of March 17, 1997, a person of skill in the art would not have been able to identify or describe the specific epitope that a monoclonal antibody will recognize on a DR5 protein antigen before the antibody had actually been produced and characterized. (AX-1086, ¶ 51).

98. Once a reference antibody has been produced and identified, a person of ordinary

skill in the art could determine the specific amino acid sequences present in the two polypeptide chains of the antibody. (AX-1086, ¶ 55).

99. Equipped with the discussed in paragraph 98, a particular binding specificity can be associated with a particular amino acid sequence and antibody structure. (AX-1086, ¶ 55).

100. As of March 17, 1997 and July 29, 1997, a person of ordinary skill in the art would not have been able to define the amino acid sequence or three-dimensional structure of an antibody necessary to cause the antibody to bind to a particular epitope on a DR5 without structural information derived from a pre-existing reference antibody that exhibits the desired epitope-binding specificity. (AX-1086, ¶ 56; AX-1055; and AX-1054, Abstract ("Certain 'lottery-like' aspects of these genetic processes add to the combinatorial possibilities that are characteristic of the humoral immune system.")).

101. As of March 17, 1997 and July 29, 1997, a person of ordinary skill in the art would not have been able to identify or describe the location of an epitope on a DR5 to which an antibody must bind in order for the antibody to act as an agonist or an antagonist of DR5 without use of a reference antibody that exhibits an epitope-binding specificity that confers on the antibody the capacity to act as an agonist or antagonist of DR5. (AX-1086, ¶ 57).

102. As of March 17, 1997 and July 29, 1997, a person of ordinary skill in the art would not have been able to determine, using only a deduced amino acid sequence of a DR5 polypeptide, the location of an epitope on the DR5 protein to which an antibody must bind to enable the antibody to act as an agonist or antagonist of the DR5. (AX-1086, ¶ 57 and AX-1056, p. 14435, col. 2, ¶¶ 2 and 3).

C. <u>Monoclonal Antibodies Distinguished from Polyclonal Antibodies</u>

103. By March 17, 1997 and July 29, 1997, a person of ordinary skill in the art would

have considered it practically impossible to identify and isolate individual antibody molecules from polyclonal antisera, or to determine specific functions possessed by an individual antibody present in the polyclonal antisera. (AX-1086, ¶ 58).

104. By March 17, 1997, possession of a polyclonal antiserum would not have provided a person of ordinary skill in the art with a particular reference antibody that could be characterized to determine its structure, or otherwise used to produce additional copies of that particular antibody and, in particular, a person of ordinary skill in the art would have faced problems obtaining sufficient quantities of a reference antibody. (AX-1086, ¶ 59).

105. This would have been particularly true when no techniques were known for selecting the specific antibody out of a polyclonal antiserum containing many other antibodies that bind to the same antigen. (AX-1086, ¶ 59).

106. As of March 17, 1997, a person of ordinary skill in the art would have been unable to use a polyclonal antiserum to produce cell lines that would yield individual desired monoclonal antibodies. (AX-1086, ¶ 59).

107. By March 17, 1997, it was well accepted that monoclonal antibody compositions offered several significant benefits over polyclonal antisera in diagnostic, therapeutic and analytical applications. (AX-1086, ¶ 60 and AX-1050, p. 1797, col. 2, section entitled "Polyclonal vs. Monoclonal Antibody.").

108. Because a monoclonal antibody composition is homogeneous, it will exhibit a uniform binding profile and thus will induce a more consistent biological effect if administered to a mammal or used in a cell-based assay. (AX-1086, ¶ 60 and AX-1050, p. 1797, col. 2, section entitled "Polyclonal vs. Monoclonal Antibody.").

109. A polyclonal antiserum may exhibit diverse binding specificities and effector

functions, because antisera contain many different antibodies, each having distinct binding characteristics and isotypes. (AX-1086, ¶ 60 and AX-1050, p. 1797, col. 2, section entitled "Polyclonal vs. Monoclonal Antibody.").

110. A polyclonal antiserum may induce many, often mutually exclusive, biological effects when administered to a patient or used in a cell-based assay. (AX-1086, ¶ 60).

111. The diversity in biological responses may also vary with each batch of sera tested, even when batches are derived from a single immunization of an animal. (AX-1086, ¶ 60 and AX-1049, p. 511, col. 2, ¶ 2).

V. Structure of Cell Surface Receptors and Brief Overview of TNFR Family Members

A. General Observations on Cell Surface Receptors

112. A given cell surface receptor may signal through several distinct signal transducing pathways. In some cases, these effector pathways may act synergistically, in some cases they act additively, and in some cases they may oppose each other. (AX-1086, ¶ 61; AX-1046).

113. This is particularly relevant for signaling of TNFR family members which are known to have highly pleiotropic functions. (AX-1086, ¶ 61).

B. TNFR Family Overview

114. By March 17, 1997, there were a number of known members of the TNFR family, including: **TNFR1** (also known as CD120a, p55-TNFR, TNFR60, DR1); **TNFR2** (also known as CD120b, p75-TNFR, TNFR80); **LTβR** (also known as CD18, TNFR3); **OX40** (also known as CD134, ACT35); **Fas** (also known as CD95, Apo-1, DR2); **CD27** (also known as Tp55, S152); **CD30** (also known as Ki-1, D1S1665E); **CD40**; **4-1BB** (also known as CD137, ILA); **DR3** (also known as WSL-1, TRAMP, Apo-3, LARD); and **p75 NGFR** (also known as p75-NTR). (AX-

1086, ¶ 63; NX-2053, p.48, Table I; AX-1058, p.3380, Fig. 1; and AX-1037, p. 1, lns. 19-23, 26-29 and p. 2, lns. 28-31).

115. By March 17, 1997, it was known that TNFR family members and their respective cognate ligands are associated with a diverse range of cellular mechanisms and biological effects, including: cellular proliferation, induction or suppression of apoptosis, induction or suppression of other mechanisms of necrotic cell death, promotion or inhibition of inflammation, activation of the NF-κB and JNK intracellular pathways, co-stimulation and regulation of T-cell activities (including CD4 memory T cells and CD8 T cells), immune privilege functions, and activation and regulation of B cells and myeloid cells. (AX-1086 ¶ 64; NX-2053, p.48, Table I; AX-1046, Abstract; AX-1059, Abstract; AX-1078, Abstract; and AX-1060, Abstract).

116. The '846 application discloses that the effects of the TNF family of ligands and receptors "are varied and influence numerous functions, both normal and abnormal, in the biological processes of the mammalian system" and are "among the most pleiotropic cytokines, inducing a large number of cellular responses...." (AX-1086, ¶ 64 and AX-1037, p. 3, lns. 15-17 and p. 26, lns. 5-8).

117. By March 17, 1997, a person of ordinary skill in the art would have known that TNFR family members play a role in the observed biological effects through unique cognate ligand-receptor binding characteristics, rather than through undifferentiated interactions between TNF ligand family members and TNFR family members. (AX-1086, ¶ 66 and NX-2053, Abstract).

118. By March 17, 1997, it had been shown that many TNFR family members interact with cognate ligands on a "one receptor/one ligand" basis (e.g., CD27/CD27L, CD30/CD30L,

CD40/CD40L, 4-1BB/4-1BBL, OX40/OX40L (gp34), FAS/FASL), while others show more complex types of interactions. (AX-1086, ¶ 66 and AX-1058, p.3394, col. 1, ¶ 3).

119. By March 17, 1997, a person of ordinary skill in the art would have known that other TNFR family members, such as TNFR1, TNFR2 and LTβR, could bind more than one ligand. (AX-1086, ¶ 66).

120. By March 17, 1997, a person of ordinary skill in the art would have known that certain ligands could bind to more than one member of the TNFR family. (AX-1086, ¶ 66).

VI. <u>Requirements of the Monoclonal Antibodies of the Counts</u>

121. The antibodies that are the subject of the Counts are identified by reference to two functional properties. (AX-1086, ¶ 67).

122. One of the functional properties of the Counts is that the antibody binds to an extracellular domain sequence of a DR5 polypeptide (*i.e.*, amino acids 1 to 133 of SEQ ID NO:2). (AX-1086, ¶ 67).

123. This binding function can be evaluated without knowledge of the functions that a DR5 polypeptide modulates or is involved in. (AX-1086, ¶ 67).

124. The second functional property of the Counts is that the antibody functions as an "agonist" or an "antagonist" of a DR5. (AX-1086, ¶ 68).

125. This requirement refers to the biological effect(s) or responses exhibited when a cognate ligand binds to a DR5 in a setting where the levels of expression of the receptor are not artificially manipulated. (AX-1086, ¶ 68).

126. A person of ordinary skill in the art would have recognized that the terms "agonist" and "antagonist" had well accepted meanings by March 17, 1997. (AX-1086, ¶ 69).

127. A representative definition of the terms "agonist" and "antagonist" is provided in

a widely used textbook, Goodman and Gilman's, The Pharmacological Basis of Therapeutics (Ninth Edition (1996), p. 29 bridging p. 30):

> Drugs that bind to physiological receptors and mimic the effects of the endogenous regulatory compounds are termed agonists. Other drugs bind to receptors and do not mimic, but interfere with, the binding of the endogenous agonist. Such compounds, which are themselves devoid of intrinsic regulatory activity, but which produce effects by inhibiting the action of an agonist (e.g., by competition for agonist binding sites), are termed antagonists. [AX-1086, ¶ 69 and AX-1064, pp. 29-30].

128. By March 17, 1997, it was well known that many TNFR family members can mediate intracellular signaling functions in cells. (AX-1086, ¶ 70; NX-2053, Table I; and AX-1065, p. 357, Fig. 1).

129. Intracellular signaling results from binding of a cognate ligand (*i.e.*, endogenous agonist) to the TNFR family member residing on the cell surface. (AX-1086, ¶ 70 and AX-1058, p. 3394, col. 1, ¶ 3).

130. The intracellular signals, in turn, can induce a variety of observable biological effects in the cell. (AX-1086, ¶ 70).

131. By March 17, 1997, it was further known that observable biological effects exhibited by a cell in response to signaling induced by binding of a cognate ligand to a TNFR family member in its endogenous cellular environment could also be induced through (i) use of agents that do not interact with the receptor or (ii) by artificially manipulating the levels of expression of the receptor on the cell. (AX-1086, ¶ 71; AX-1066, Abstract; and NX-2065, p. 991, col. 3, ¶ 2).

132. However, it was further known that such biological effects may not be the same biological effects as those that result from binding of the cognate ligand. (AX-1086, ¶ 71 and NX-2072).

133. In view of these points, a person of ordinary skill in the art, as of March 17, 1997 and as of July 29, 1997, would have understood that a monoclonal antibody that acts as an agonist of a DR5, would, when it binds to a DR5, activate the receptor to induce the signaling effects that are induced when a cognate ligand binds to a DR5 that is expressed on the cell surface under conditions that do not artificially manipulate the natural levels of expression of the receptor. (AX-1086, ¶ 72).

134. A person of ordinary skill in the art, as of March 17, 1997, also would have understood that a monoclonal antibody that acts as an antagonist of a DR5 would, upon binding to an extracellular domain of that DR5, inhibit the signaling effects that are induced when a cognate ligand binds to a DR5 being expressed on the cell surface under conditions that do not artificially manipulate the natural levels of expression of the receptor. (AX-1086, ¶ 73).

A. What is Needed to Describe a Monoclonal Antibody that Exhibits Particular Functional Properties

135. By March 17, 1997, and by July 29, 1997, a person of ordinary skill could adequately identify and characterize a monoclonal antibody meeting the requirements of Count 1 or Count 2 by describing the structure of a DR5 antibody that is necessary for it to exhibit the specific binding function that causes the antibody to function as an agonist or an antagonist, such as the amino acid sequence of at least those portions of the variable domains of the light and heavy immunoglobulin chains that are necessary to define the epitope binding specificity of the antibody, or the sequence of a nucleic acid encoding such portions of the light and heavy chains. (AX-1086, ¶ 74)

136. By March 17, 1997, and by July 29, 1997, a person of ordinary skill could adequately identify and characterize a monoclonal antibody meeting the requirements of Count 1 or Count 2 by describing a hybridoma or other cell line that produces a representative DR5

antibody that exhibits the specific binding function that causes the antibody to function as an agonist or antagonist. (AX-1086, ¶ 74).

137. To design and perform assays that could be used to identify monoclonal antibodies meeting the requirements of Count 1 or Count 2, a person of ordinary skill in the art, by March 17, 1997 and by July 29, 1997, first would need to know the consequences of binding of a cognate ligand to a DR5 as it is expressed on the surface of a cell under conditions that do not entail artificially manipulating natural expression levels of the receptor. (AX-1086, ¶ 76).

138. If observable biological effects in a cell are being used to characterize the monoclonal antibody as an agonist or an antagonist of a DR5, a person of ordinary skill in the art would need to know the biological effects that are characteristic of signaling caused by cognate ligand binding to a DR5 (in the case of an agonist) or from inhibition of the signaling resulting from cognate ligand binding to the receptor (in the case of an antagonist). (AX-1086, ¶ 77).

139. Without knowing the biological effects that are characteristic of signaling caused by cognate ligand binding to a DR5, a person of ordinary skill in the art could not have attributed the observable biological effects to an agonistic or antagonistic interaction between the monoclonal antibody and a DR5 as it is expressed on the cell surface. (AX-1086, ¶ 77).

140. A person of ordinary skill in the art must have been able to correlate the observable biological effects exhibited when a test molecule is incubated with cells expressing a DR5 to interactions between the test molecule and a DR5 to ensure that the biological consequences result from receptor-mediated signaling, rather than from other non-receptor interactions with the cell. *See*, AX-1086, ¶ 78 and AX-1066, Abstract, last sentence ("[t]hese results indicate that antineoplastic treatments [e.g., cisplatin] induce apoptosis through a Fas-independent pathway even though fas- and chemotherapy-induced pathways converge on

common downstream apoptotic effector molecules.")

141. A DNA damaging agent could trigger apoptosis without having any effect on a DR5. (AX-1086, ¶ 78).

142. If a person of ordinary skill cannot establish that the observable biological effects result from receptor-mediated signaling, such a person would be unable to characterize a molecule being tested as an agonist or an antagonist of a DR5, as those terms require the observable biological effects to result from ligand-receptor-mediated signaling (in the case of the agonist) or inhibition of those signals (in the case of an antagonist). (AX-1086, ¶ 78).

143. As of March 17, 1997 and July 29, 1997, a person of ordinary skill in the art could not have screened randomly produced monoclonal antibodies or antibody-producing cells to identify and select monoclonal antibodies that bind to an extracellular domain of a DR5 and act as an agonist or as an antagonist of that DR5 if that person had not established an accurate correlation between a measurable biological effect being detected through use of the assay, and where the result of activation of a DR5 by a cognate ligand of DR5 was not known. (AX-1086, ¶ 79).

144. As of March 17, 1997 and July 29, 1997, a person of ordinary skill would need to know the identity of a cognate ligand of a DR5 to determine if a monoclonal antibody could inhibit or reduce the signaling effects associated with cognate ligand binding to a DR5. (AX-1086, ¶ 80).

B. The Descriptions in the '846 Application of Agonists and Antagonist Are Inconsistent with Well-Accepted Meanings and Show that the '846 Application Does Not Describe Agonist or Antagonistic Monoclonal Antibodies of a DR5

145. The discussions of agonists contained in the '846 application are inconsistent with the commonly accepted meaning of "agonist" that was known to a person of skill in the art by

March 17, 1997. For example, at page 27, lines 3-6, the application states that "...the present invention is directed to a method for enhancing apoptosis induced by TNF-family ligand, which involves administering...an effective amount of DR5 ligand, analog or an agonist capable of increasing DR5 mediated signaling." And at p. 27, lines 31-34, the '846 application states that "inhibition or enhancement of the signal generated by the ligand indicates that the compound is an antagonist or agonist of the ligand/receptor signaling pathway." However, the '846 application goes on to provide a list of potential agonist molecules that a person of ordinary skill in the art would have considered inconsistent with these passages and misleading in light of the correct understanding of the term agonist. (AX-1086, ¶ 83 and AX-1037, page 27, lines 3-6 and 31-34).

146. For example, on p. 27, lines 18-19 the '846 application states that "by agonist is intended naturally occurring and synthetic compounds capable of enhancing or potentiating apoptosis." (AX-1037, page 27, lines 18-19). It then states, on page 29, lines 7-19, that examples of agonists include:

> TNF family ligand peptide fragments, transforming growth factor, neurotransmitters (such as glutamate, dopamine, N-methyl-D-aspartate), tumor suppressors (p53), cytolytic T cells and antimetabolites. Preferred agonist[s] include chemotherapeutic drugs such as, for example, cisplatin, doxorubicin, bleomycin, cytosine arabinoside, nitrogen mustard, methotrexate and vincristine. Others include ethanol and amyloid peptide. [AX-1037, page 29, lines 7-19 and AX-1086, ¶ 84].

147. By March 17, 1997, it had been shown that many of the compounds that are identified in the '846 application as "preferred" agonists either do not induce cell death through apoptosis, or do not induce apoptosis through a selective binding to a TNFR. (AX-1086, ¶ 85; AX-1074, p. 787, col. 1, ¶ 3 ("The cytotoxicity of cisplatin is believed to be due to the formation of DNA adducts, which include DNA-protein cross-links, DNA monoadducts, and interstrand and intrastrand DNA cross-links"); and AX-1075, p. 1689, col. 1, ¶ 2 ("Early morphological studies

have shown that VCR [vincristin] destroys spindle microtubules… suggesting a specific interaction between VCR and the microtuble protein."))

148. Because the compounds that are identified as "preferred" agonists would not induce apoptosis through an interaction with a DR5 that mimics the binding of a cognate ligand, a person of ordinary skill in the art would not have considered these molecules to be "agonists" of a DR5. (AX-1086, ¶ 85).

C. Identification of a cDNA and Deduced Amino Acid Sequence of a DR5 Would Not Have Allowed a Person of Ordinary Skill in the Art to Determine If An Antibody, or Other Molecule, Was An Agonist or Antagonist of a DR5

149. The '846 application provides no information derived from actual experimental characterization or testing of a DR5 polypeptide. (AX-1086, ¶ 86 and AX-1037).

150. The '846 application does not provide any indication that any DR5 polypeptide had been expressed. (AX-1086, ¶ 86 and AX-1037).

151. The '846 application does not identify a cognate ligand of DR5. (AX-1086, ¶ 87 and AX-1037).

152. At page 31, lines 4 to 10, the '846 application lists TNF family ligands that had been identified in the literature prior to March 17, 1997. (AX-1086, ¶ 87 and AX-1037, p. 31, lns. 4-10).

153. There is no indication at page 31, lines 4 to 10 of the '846 application, or anywhere else in the '846 application, that one or more of the listed TNF family ligands that had been identified in the literature prior to March 17, 1997 is a cognate ligand of a DR5. (AX-1086, ¶ 87 and AX-1037, p. 31, lns. 4-10).

154. A simple list of all TNF family ligands known as of March 17, 1997 would provide no guidance to a person of ordinary skill in the art as to which, if any, of the listed ligands

was a cognate ligand of a DR5. (AX-1086, ¶ 87).

155. A person of ordinary skill in the art, as of March 17, 1997, would have read the reference in the alternative to "DR5 ligands" and TRAIL to mean that DR5 ligand is most likely a molecule that is distinct from TRAIL. (AX-1086, ¶ 88 and AX-1037, p. 31, lns. 4-9).

156. Information that TRAIL is a cognate ligand of a DR5 was not reported in the published literature until after July 29, 1997. (AX-1086, ¶ 88; NX-2021; and NX-2022).

157. The '846 application does not report any data from testing of the binding of any TNF family ligand, in particular TRAIL, to cells expressing DR5. (AX-1086, ¶ 89 and AX-1037).

158. The '846 application does not describe any observed biological effects derived from binding of any TNF family ligand to a DR5. (AX-1086, ¶ 89 and AX-1037).

159. The '846 application does not identify or describe cell lines (or deposits thereof) that express DR5 and in which apoptosis or any other biological effects can be induced upon binding of a cognate ligand or an agonistic monoclonal antibody to a DR5. (AX-1086, ¶ 90 and AX-1037).

160. As of March 17, 1997, a person of ordinary skill in the art would not have been able to determine if a given monoclonal antibody was acting as an agonist or an antagonist of a DR5 by simply adding the antibody to cultures containing DR5-transfected cells and observing the biological effect(s) the antibody exerts on those cells. (AX-1086, ¶ 92).

161. The lack of any information in the '846 application correlating apoptosis or any other cellular response to a cognate ligand binding to a DR5 would have precluded a person of ordinary skill in the art from doing so. (AX-1086¶ 93 and AX-1037).

162. The over-expression of a TNFR may potentiate signaling effects that would not

otherwise occur upon ligand binding. (AX-1086, ¶ 94).

163. Without information that allows a person of ordinary skill in the art to correlate an observed biological effect to receptor-ligand signaling or inhibition of such signaling, a person of ordinary skill in the art could not have determined as of March 17, 1997 and July 29, 1997 whether the observed biological effect of an antibody was attributable to agonistic or antagonistic interactions with the receptor. (AX-1086, ¶ 94).

164. The '846 application contains no information that establishes that a DR5 overexpression assay was actually conducted. There are not any results of such an assay in the '846 application. An overexpression assay, standing alone, would not have been the preferred method for demonstrating the apoptosis inducing activity of a new, previously uncharacterized death domain containing TNFR. (AX-1086, ¶ 95; NX-2064, ¶ 25; and AX-1037).

165. A person of ordinary skill in the art, as of March 17, 1997, would have known that cognate ligand binding to death-domain containing TNFR family members was associated with a variety of biological effects in the cell expressing the TNFR family member other than apoptosis. (AX-1086, ¶ 98).

166. TNFα binding to TNFR1 activates the NF-κB pathway, which can operate to promote cell survival, and inhibit apoptosis, when it binds to its cognate ligand, TNFα. (AX-1086, ¶ 98; AX-1046, Abstract ("...while activation of NF-κB protects against TNF-induced apoptosis"); AX-1070, p. 784, col. 1, ¶ 1 ("However, a dose-dependant increase in cell survival was seen when RelA [NF-κB] was provided, with virtually complete protection at the highest dose (Fig. 3)"); AX-1071, Abstract ("[t]hese findings suggest that a negative feedback mechanism results from TNFα signaling in which NF-κB activation suppresses the signals of cell death"); and AX-1072, Abstract ("[t]he activation of the transcription factor ...NF-κB by tumor necrosis factor

(TNF) ...was found to protect from cell killing")).

167. The '846 application does not describe any antibody in terms that a person of ordinary skill would have found useful to identify and describe a particular agonist or antagonist antibody of a DR5. The '846 application does not provide the amino acid sequence of the heavy and light chains of an antibody, or a nucleic acid sequence encoding such heavy and light chains. (AX-1086, ¶ 99 and AX-1037).

168. The '846 application does not describe a hybridoma or other type of cell line that produces an antibody that binds to an extracellular domain of the DR5 polypeptide and acts as an agonist or an antagonist of a DR5. (AX-1086, ¶ 99 and AX-1037).

169. A person of ordinary skill in the art would not have considered the '846 application to provide a description of any particular agonist antibody of a DR5. (AX-1086, ¶ 100 and AX-1037).

170. There is only one reference to antagonist antibodies in the '846 application; namely in a single sentence on page 27, lines 16-17. A person of ordinary skill in the art would not have considered this disclosure to provide a description of any particular antagonist antibody of a DR5. (AX-1086, ¶ 101 and AX-1037, p. 27, lns. 16-17).

D. The '846 Application Does Not Describe Techniques That Will Identify a Monoclonal Antibody that Acts As An Agonist or Antagonist of DR5

171. The '846 application does not contain any description of any assays or other biological evaluations that involved contacting cells expressing DR5 with a cognate ligand of DR5. (AX-1086, ¶ 103 and AX-1037).

172. A person of ordinary skill in the art would not have considered the assays presented in the '846 application to have described any attributes of an agonistic or antagonistic antibody. (AX-1086, ¶ 104 and AX-1037).

173. In particular, the assays described at page 27, lines 25 to page 29, line 7 of the '846 application would not have provided sufficient information to allow a person of ordinary skill in the art to identify an agonist or antagonist antibody of a DR5. (AX-1086, ¶ 104 and AX-1037, p. 27, ln. 25 to p. 29, ln. 7).

174. The '846 application does not describe the use of controls for any of the assays it discloses. (AX-1086, ¶ 104 and AX-1037).

175. In particular, the '846 applications fails to describe, for any of the assays it lists, an appropriate control to ensure, for example, that the biological effect observed in an assay is specific to DR5. (AX-1086, ¶ 104 and AX-1037).

176. The first assay, described at page 27, lines 25-33 (AX-1037, p. 27, lns. 25-33), is a melanophore screening assay as described in PCT WO/92/01810. (AX-1086, ¶ 105 and AX-1073).

177. The assay described at page 27, lines 25-33 identifies compounds that act as an agonist or antagonist of G-protein coupled cell surface receptors. (AX-1086, ¶ 105 and AX-1037, p. 27, lns. 25-33).

178. A person of ordinary skill in the art, as of March 17, 1997, and as of July 29, 1997, would have recognized that DR5 is not a G-protein coupled cell surface receptor. (AX-1086, ¶ 105).

179. The assay described at page 27, lines 25-33 would not have informed a person of ordinary skill in the art anything about apoptosis induction or inhibition thereof. (AX-1086, ¶ 105 and AX-1037, p. 27, lns. 25-33).

180. The assay described at page 27, lines 25-33 would not and could not have informed a person of ordinary skill in the art whether an isolated antibody would act as an agonist

or antagonist of DR5. (AX-1086, ¶ 105 and AX-1037, p. 27, lns. 25-33).

181. The assay described at page 27, lines 25-33 would also require the use of a cognate ligand. (AX-1086, ¶ 105 and AX-1037, p. 27, lns. 25-33).

182. The assay described at page 27, line 34 to page 28, line 3, of the '846 application, focuses on measurement of extracellular pH changes caused by receptor activation. (AX-1086, ¶ 106 and AX-1037, p. 27, ln. 34 to p. 28, ln. 3).

183. A person of ordinary skill in the art would have recognized that there is no information in the '846 application that indicates whether a pH change is observed upon activation of a DR5, or the nature of any such pH change. (AX-1086, ¶ 106 and AX-1037).

184. A person of ordinary skill could not have used the assay techniques described at page 27, line 34 to page 28, line 3 to evaluate an isolated antibody to a DR5 to determine if the isolated antibody would act as an agonist or antagonist of that DR5. (AX-1086, ¶ 106 and AX-1037, p. 27, ln. 34 to p. 28, ln. 3).

185. To conduct the assay described at page 28, lines 4 to 9, of the '846 application, the application discloses, "the receptor oocytes may then be contacted with the receptor ligand and a compound to be screened, followed by detection of inhibition or activation of a calcium signal in the case of screening for compounds which are thought to inhibit activation of the receptor." (AX-1086, ¶ 107 and AX-1037, p. 28, lns. 4-9).

186. The '846 application does not show that DR5 ligation can cause calcium flux. (AX-1086, ¶ 107 and AX-1037).

187. A person of ordinary skill in the art could not have practiced the assay described at page 28, lines 4 to 9 to determine if an isolated antibody would act as an agonist or an antagonist of DR5. (AX-1086, ¶ 107 and AX-1037, p. 28, lns. 4-9).

188. The assay described at page 28, lines 10 to 15 of the ‘846 application, involves detection of a phospholipase enzymatic activity. (AX-1086, ¶ 108 and AX-1037, p. 28, lns. 10-15).

189. A person of ordinary skill in the art would have recognized that the assay described at page 28, lines 10 to 15 requires use of a cognate ligand, which is not disclosed in the ‘846 application. (AX-1086, ¶ 108 and AX-1037, p. 28, lns. 10-15).

190. A person of ordinary skill in the art would also have recognized that the assay described at page 28, lines 10 to 15 could not have been used to determine if a cognate ligand of a DR5 or an isolated DR5 antibody would induce DR5-mediated apoptosis because phospholipase activity is not specifically correlated to, and is thus not indicative of, apoptosis induction. (AX-1086, ¶ 108 and AX-1037, p. 28, lns. 10-15).

191. The assay described at page 28, lines 15 to 25 of the ‘846 application, involves measurement of competitive inhibition of binding of a labeled ligand to the receptor. (AX-1086, ¶ 109 and AX-1037, p. 28, lns. 15-25).

192. A person of ordinary skill in the art would have recognized that the assay described at page 28, lines 15 to 25, requires use of a cognate ligand of a DR5, which is not identified in the ‘846 application. (AX-1086, ¶ 109 and AX-1037, p. 28, lns. 15-25).

193. A person of ordinary skill in the art could not have used the assay described at page 28, lines 15 to 25 to determine if an isolated antibody would act as an agonist or antagonist of a DR5 . (AX-1086, ¶ 109 and AX-1037, p. 28, lns. 15-25).

194. At page 28, lines 26-28 (AX-1037, p. 28, lns. 26-28), the ‘846 application refers to an assay described in a publication by Tartaglia and Goeddel, *J. Biol. Chem.* 267(7):4304-4307 (1992). (AX-1086, ¶ 110 and NX-2072).

195. The Tartaglia paper describes research performed on the TNFR family member, TNFR1. (AX-1086, ¶ 110 and NX-2072).

196. One assay disclosed in the Tartaglia paper involved screening transfected L929 cells to detect cytotoxicity resulting from addition of anti-TNFR1 monoclonal antibodies. (AX-1086, ¶ 110 and NX-2072).

197. A person of ordinary skill in the art would have recognized that the TNFR1-transfected cells were treated with cycloheximide in the assay. (AX-1086, ¶ 110 and NX-2072).

198. By March 17, 1997, a person of ordinary skill in the art would have known that cycloheximide inhibited activation of the anti-apoptotic NF-κB pathway, thereby artificially inhibiting the (innate) NF-κB pathway in the cells which would otherwise block apoptotic activity. (AX-1086, ¶ 110 and AX-1046).

199. A person of ordinary skill in the art would have recognized that the assay described on page 28, lines 26-28 of the '846 application required use of the cognate ligand of TNFR1 as a control. (AX-1086, ¶ 110 and AX-1037, p. 28, lns. 26-28).

200. A person of ordinary skill in the art, by March 17, 1997, could not have used the assay described on page 28, lines 26-28 of the '846 application to determine if an isolated antibody would act as an agonist or an antagonist of a DR5. (AX-1086, ¶ 110 and AX-1037, p. 28, lns. 26-28).

201. The assay mentioned at page 28, line 29 to page 29, line 6 of the '846 application, is a competitive binding assay that requires use of a "TNF-family ligand" and the candidate compound. (AX-1086, ¶ 111 and AX-1037, p. 28, ln. 29 to p. 29, ln. 6).

202. The assay mentioned at page 28, line 29 to page 29, line 6 requires use of a cognate ligand of the DR5 to measure the degree of competition in binding between the test

molecule and the cognate ligand. (AX-1086, ¶ 111 and AX-1037, p. 28, ln. 29 to p. 29, ln. 6).

203. A person of ordinary skill in the art, as of March 17, 1997, could not have used the assay mentioned at page 28, line 29 to page 29, line 6 to identify an isolated antibody that would act as an agonist or an antagonist of a DR5. (AX-1086, ¶ 111 and AX-1037, p. 28, ln. 29 to p. 29, ln. 6).

E. A Person of Ordinary Skill in the Art Could Not Have Predicted That A TNFR Family Member Will Induce Apoptosis Based on The Presence of a Death Domain

204. By March 17, 1997, a person of ordinary skill in the art would have known that "death domains" are sequence structure motifs involved in protein-protein interactions and are found in the intracellular regions of a variety of proteins, including FADD (MORT1), TRADD, RIP, Ankryn, the ankryn-related proteins UNC-5 and UNC-44, PELLE, TUBE, DAP-kinase, myD88, N5, p84, pRb, NF-κB2/p100 as well as some but not all members of the TNFR family. (AX-1086, ¶ 112; AX-1076, p.343, Fig. 2; and AX-1077, p. 322, Fig. 1).

205. A person of ordinary skill in the art would have understood that death domain structures are not exclusive to the TNFR family, and that the presence of a death domain structure in a newly identified molecule would not, standing alone, warrant classification of the molecule as a new member of the TNFR family. (AX-1086, ¶ 112).

206. By March 17, 1997, a person of ordinary skill in the art would have understood that the mere presence of a death domain structure in a protein does not reveal the function or activity of the molecule, and in particular, does not reveal that the molecule will induce apoptosis upon ligand binding, or even play a role in apoptosis. (AX-1086, ¶ 113).

207. By March 17, 1997, it had been shown that several death domain-containing proteins were not implicated in cell-death induction. (AX-1086, ¶ 113 and AX-1076, p.344, Fig.

2 ("so far there is no evidence implicating the ankyrins, myD88, TUBE, PELLE or N5 in cell-death induction")).

208. Before March 17, 1997, it was well established that the biological effects exhibited upon ligand binding to TNFR1, Fas and DR3 varied. (AX-1086, ¶ 116).

209. The '846 application at page 3, lines 7-9, states "TNFR-1 can signal an array of diverse biological activities – many of which stem from its ability to activate NF-κB." (AX-1086, ¶ 116 and AX-1037, p. 3, lns. 7-9).

210. Before March 17, 1997, TNFR1 and its cognate ligand, TNFα, were known in the art to be associated with different biological functions ranging from cell differentiation and proliferation to inflammation to apoptosis induction. (AX-1086, ¶ 117 and AX-1046, Abstract, 1st sentence).

211. Before March 17, 1997, it had been established that activation of TNFR1 by binding of TNFα ordinarily blocks apoptosis. (AX-1086, ¶ 117).

212. By March 17, 1997, a person of ordinary skill in the art would have been familiar with various work, which showed that activation of TNFR1 by TNFα binding under physiological conditions, does not result in apoptosis unless additional, artificial measures are taken to inhibit the activation of NF-κB by the same ligand-receptor interaction. (AX-1086, ¶ 117 and AX-1046).

213. Several studies published before March 17, 1997, had demonstrated that activation of TNFR1 served to activate the NF-κB pathway, which was known, before March 17, 1997, to <u>inhibit</u> ligand-mediated apoptosis. (AX-1086, ¶ 117; AX-1046; AX-1070; AX-1071; and AX-1072).

214. A person of ordinary skill in the art by March 17, 1997, would have understood that cognate ligand activation of TNFR1 in many cells types under many conditions

predominantly promoted cell survival, through NF-κB activation, rather than inducing apoptosis. (AX-1086, ¶ 117).

215. By March 17, 1997, it was known that Fas receptor could induce proliferation of certain cell types, in addition to an ability to stimulate apoptosis upon binding of a cognate ligand, FasL. (AX-1086, ¶ 118; AX-1060, pp. 705-706, Fig. 6; and AX-1078, p. 2233, Fig. 1).

216. By March 17, 1997, it was known that Fas ligand activation of the Fas receptor recruited the intracellular adaptor molecule FADD and that FADD was not typically capable of initiating the activation of the NF-κB pathway. (AX-1086, ¶ 118 and NX-2065, p. 990, col. 1, ¶ 1 ("Activation of CD95 [Fas] recruits the…molecule FADD. Although the central role of CD95 is to trigger apoptosis, TNFR-1 can signal an array of diverse biological activities, many of which stem from its ability to activate nuclear factor κB (NF-κB).")).

217. Another TNFR family member referred to in the '846 application, DR3, had, by March 17, 1997, been shown to play a role in induction of apoptosis and in the activation of the NF- κB pathway. (AX-1086, ¶ 119 and NX-2065).

218. By March 17, 1997, the predominant signaling associated with ligand binding to DR3 was not known, as a cognate ligand for DR3 had not yet been identified. (AX-1086, ¶ 119).

219. By March 17, 1997, the death domain-containing TNFR family member, p75 NGFR, had been shown to inhibit apoptosis upon binding by its cognate ligand, NGF. (AX-1086, ¶ 120).

220. Rabizadeh *et al.*, explain that "expression of p75 NGFR induced neural cell death constitutively when p75 NGFR was unbound; binding by NGF or monoclonal antibody, however, inhibited cell death induced by p75 NGFR." (AX-1086, ¶ 120 and AX-1068, Abstract).

221. Chapman reports that "…cell death induced by NTR (namely p75 NGFR) is

reversed rather than caused by ligand binding." (AX-1086, ¶ 120 and AX-1069, p. 216, col. 1).

222. Despite the presence of a death domain that had a sequence identity of approximately 27% to the death domains of TNFR1 and Fas, apoptosis was not induced in the same manner upon agonist binding (*i.e.*, NGF or agonist antibody) to NGFR. (AX-1086, ¶ 120 and AX-1069, p.216, col. 2, § 3.1).

223. The '846 application provides little discussion regarding the p75-NGFR. (AX-1086, ¶ 121 and AX-1037).

224. The '846 application does not contain information presenting computer-based sequence comparisons of a DR5 sequence to the NGFR sequence. (AX-1086, ¶ 121 and AX-1037).

225. The '846 application does not discuss the biological effects induced by ligand binding to NFGR that had been reported in the scientific literature by March 17, 1997. (AX-1086, ¶ 121 and AX-1037).

226. Before March 17, 1997, researchers (including Dr. John Reed) had identified a region within the intracellular domain of CD40 that shared some structural similarity with other known death domains. (AX-1086, ¶ 124; AX-1080; and AX-1081).

227. It had been reported, prior to March 17, 1997, that CD40 had an intracellular region that shared sequence homology with the death domains of NGFR (22%), TNFR1 (26-31%) and Fas (39-41%). (AX-1086, ¶ 124; AX-1080, p.161, Fig. 1; and AX-1081, p. 113).

228. Prior to March 17, 1997, it had been suggested, that CD40 played a role in cell survival and cell proliferation, and protected against apoptosis in certain cell types. (AX-1086, ¶ 124; AX-1082; and AX-1083, Abstract).

229. As of March 17, 1997, knowledge that a TNFR family member contained a death

domain would not have provided a person of ordinary skill in the art a basis for reasonably predicting that the receptor would induce apoptosis upon cognate ligand binding. (AX-1086, ¶ 125).

F. Mechanisms of Apoptosis Known by March 17, 1997

230. It was known by March 17, 1997 that in order to stimulate an intracellular signal upon ligand binding, a TNFR family protein needed to recruit certain intracellular adaptor proteins. (AX-1086, ¶ 126 and AX-1065, p. 357).

231. It was known by March 17, 1997, that signaling by TNFR1 was mediated by an intracellular molecule known as TNFR1-associated death domain protein (TRADD). (AX-1086, ¶ 126).

232. By March 17, 1997, intracellular signaling by Fas was known to be mediated by direct binding of a distinct different adaptor protein called Fas-associated death domain-containing molecule (FADD). (AX-1086, ¶ 126; AX-1084, Abstract; and AX-1079, Abstract).

233. By March 17, 1997, it was known that the identity of the intracellular adaptor molecule recruited by a receptor makes a critical difference as to whether (i) apoptosis is induced (FADD and caspase 8), (ii) apoptosis is inhibited (RIP and NF-κB), or (iii) some other cellular signaling pathway is activated (TRAF2 and JNK). (AX-1086, ¶ 127).

234. Which signaling pathway or pathways would be activated or what resulting biological effect would occur could not have been predicted based on comparisons or alignments of receptor (or death domain) sequence structures. (AX-1086, ¶ 127).

G. Sequence Structure Identity or Similarity Does Not Establish Functions of TNFRs With Death Domains

235. The ‘846 application provides a sequence alignment of the DR5 amino acid sequence to those of TNFR1, Fas and DR3. (AX-1086, ¶ 128 and AX-1037, p. 5, lns. 8-13 and

Figure 2).

236. The '846 application reports that "the DR5 polypeptide of the invention shares the greatest degree of homology with human TNFR1, Fas and DR3..." (AX-1086, ¶ 128 and AX-1037, p. 6, lns. 29-30).

237. The '846 application suggests that a death domain is present in DR5, and comprises amino acids 324-391 of the DR5 sequence. (AX-1086, ¶ 129 and AX-1037, p. 9, lns. 13-18).

238. The '846 application notes that because the domain was predicted by computer graphics, the amino acid residues that constitute the domain "may vary slightly *(e.g.*, by about 1 to 15 residues) depending on the criteria used to define the domain." *Id.* (AX-1086, ¶ 129 and AX-1037).

239. The '846 application does not provide any analysis regarding the identity or conservation of specific amino acids within the putative death domain. (AX-1086, ¶ 130 and AX-1037).

240. By March 17, 1997, certain amino acid residues in the death domain were known to be crucial to the activity of the death domain of TNFR1. (AX-1086, ¶ 130; NX-2078, Table 2; and AX-1085, Fig. 4B).

241. The '846 application does not identify any amino acid residues within the DR5 putative death domain from which a person of ordinary skill in the art could have predicted, as of March 17, 1997, or as of July 29, 1997, which, if any, intracellular effector molecules, *e.g.*, FADD or TRADD, would directly interact with the putative death domain. (AX-1086, ¶ 130 and AX-1037).

242. A person of ordinary skill in the art would have understood that the function of a

DR5 and its mode of action could not be predicted from a sequence comparison of it to TNFR1, Fas and DR3 as of March 17, 1997, and as of July 29, 1997. (AX-1086, ¶ 131).

243. A person of ordinary skill in the art would have understood that the capacity of a given TNFR family member to activate the NF-κB pathway upon binding by a cognate ligand would have a very strong bearing on its ability to induce or inhibit apoptosis. (AX-1086, ¶ 131).

VII. The '846 Application Did Not Teach a Person of Ordinary Skill in the Art How to Make and Use an Agonist or an Antagonist Antibody to a DR5 Without Undue Experimentation

244. The information provided in the '846 application would not have provided sufficient information to a person of ordinary skill in the art to produce an isolated antibody that binds to an extracellular domain of a DR5 and acts as either an agonist or as an antagonist of DR5, without having to engage in an undue amount of research and experimentation. (AX-1086, ¶ 132 and AX-1037).

VIII. Observations on U.S. Provisional Application 60/054,021, filed July 29, 1997

245. The information added in the '021 application relative to what is contained in the '846 application includes:

- an example showing that overexpression of DR5 in the absence of a ligand results in cell killing in MCF-7 and Hela cell lines;
- an example showing that soluble DR5-Fc fusion protein bound to TRAIL but not to TNFα; and
- addition of a soluble DR5-Fc fusion protein blocked TRAIL induced apoptosis in MCF-7 cells incubated with TRAIL. [AX-1086, ¶ 142 and AX-1036].

246. A person of ordinary skill in the art would have considered the information provided in the '021 application to have been insufficient to describe an isolated antibody that binds to an extracellular domain of a DR5 and is an agonist or an antagonist of a DR5. (AX-1086, ¶ 143 and AX-1036).

247. The '021 application does not provide working examples or other guidance

pertaining to identification and selection of an isolated antibody that bind to a DR5 extracellular domain and acts as an agonist or an antagonist of a DR5. (AX-1086, ¶ 143 and AX-1036).

248. The '021 application does not provide any description of a particular antibody that was actually produced. (AX-1086, ¶ 144 and AX-1036).

249. There is no disclosure in the '021 application of an antibody that acts as an agonist of a DR5 or as an antagonist of a DR5. (AX-1086, ¶ 144 and AX-1036).

250. A person of ordinary skill in the art would not have considered the '021 application to provide a description of an antibody that is defined by any one of the Counts. (AX-1086, ¶ 145 and AX-1036).

251. The disclosure in the '021 application would not have been sufficient to enable a person of ordinary skill in this art to produce an isolated antibody that is defined by any one of the Counts without having to engage in undue experimentation. (AX-1086, ¶ 145 and AX-1036).

IX. The Board Should Carefully Scrutinize Dr. Reed's Testimony

A. District Court Decision

252. Party Ni asserts that "Dr. Reed's credentials and credibility are beyond challenge." (Ni Substantive Motion 3, p. 7, "Expert Opinion of Dr. John Reed.").

253. The testimony of Dr. Reed is discussed in a Federal District Court decision. *See*, *In re Rezulin Products Liability Litigation*, 369 F.Supp.2d 398 (S.D.N.Y. 2005) ("the *Rezulin* Decision").

254. The *Rezulin* Decision stems from a *Daubert* hearing that the Court conducted in making a determination that the testimony provided by various scientific experts, including John C. Reed, on behalf of the plaintiffs in the case was insufficiently scientifically reliable and thus excludible from consideration by the Court. *Rezulin*, 369 F.Supp.2d at 401-02; *Daubert v.*

Merrell Dow Pharmaceuticals, Inc., 516 U.S. 869 (1995).

255. The Dr. Reed providing testimony in the present interference on behalf of HGS is the same Dr. Reed whose testimony was excluded from consideration by the Court in the *Rezulin* Decision. ("Dr. Reed is the president and chief executive officer of the Burnham Institute, a research center in La Jolla, California") (NX-2064, ¶ 6). *Rezulin*, 369 F.Supp.2d at 408.

256. In the *Rezulin* Decision, Dr. Reed submitted a declaration to the Court in support of the plaintiff's scientific positions. As stated by the Court, Dr. Reed's opinion was "a major subject of this motion." *Id.*

257. In the *Rezulin* Decision, Dr. Reed's testimony also pertained to the issue of apoptosis. *Id.* ("Dr. Reed's declarations are intended to "address the evidence that Rezulin (troglitazone) induces apoptosis in human and animal cells.").

258. In rendering its decision, the Court criticized Dr. Reed's testimony. *Id.* at 413, n. 100, 417-19.

259. For example, the Court found that Dr. Reed incorrectly or misleadingly cited various articles. In so finding it stated "[t]he Court is troubled by the fact that a self-described apoptosis expert's report includes so many inaccuracies." *Id.* at 413, n. 100.

260. The Court determined that "the plaintiffs' experts have ignored a large amount of information that calls many aspects of the [proffered] theory into question." *Id.* at 425.

261. In its decision, the Court observed that "[i]n other words, the scientists have discussed only the evidence that they believed would advance the plaintiff's position. Their reports cannot be said to reflect 'the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Id.* at 426.

B. <u>Dr. Reed's Declaration in This Interference</u>

262. In his declaration, Dr. Reed states that "by March 17, 1997, three death receptors were recognized, including TNFR1 (CD120a), Fas (APO1; CD95) and DR3 (TRAMP; WSL-1; Apo-3)." (NX-2064, ¶ 20).

263. Dr. Reed did not include in his declaration the fact that by March 17, 1997, another TNFR family member, p75 NGFR, had been shown to contain a death domain and that p75 NGFR *inhibited* apoptosis upon binding by its cognate ligand. (AX-1086, ¶ 120).

264. Dr. Reed has admitted that by March 17, 1997 researchers, including himself, had identified another member of the TNFR family, CD40, that appeared to contain an intracellular region that shared some structural similarity with other known death domains. (AX-1086, ¶ 124 and NX-2064, ¶ 22).

265. According to Dr. Reed's own rationale, CD40 would have been considered a "death receptor." (AX-1086, ¶ 124 and NX-2064, ¶ 22).

266. As with p75 NGFR, it had been suggested prior to March 17, 1997, however, that CD40 played a role in cell survival and cell proliferation and protected against apoptosis in certain cell types. (AX-1086, ¶ 124).

267. In his declaration, Dr. Reed also states that "each of these receptors [referring to TNFR1, Fas and DR3] was known, by March 17, 1997 to induce cell death by apoptosis." (NX-2064, ¶ 20).

268. Dr. Reed does not acknowledge in his declaration that by March 17, 1997, it was widely recognized that some TNFR family members, including TNFR1, can inhibit rather than promote apoptosis upon ligand binding. (AX-1086, ¶¶ 98 and 117).

269. By March 17, 1997, numerous articles discussing TNFR1's apoptotic inhibiting

activity had been published in the prestigious and widely-read journals *Science* and *Cell* (*See,* AX-1070, AX-1071, AX-1072 and AX-1046), yet Dr. Reed failed to reference those publications in his Declaration. (AX-1086, ¶ 117 and NX-2064).

270. Dr. Reed also fails to explain why, in light of such information available in March 17, 1997, "a person of ordinary skill in the art would have predicted that activation of DR5 would have induced apoptosis" rather that cell survival or why "a person of ordinary skill in the art would have reasonably believed [the] assertion" in the '846 application that activation of DR5 would induce apoptosis. (NX-2064, ¶ 32).

271. In his declaration, Dr. Reed states that by March 17, 1997 it was recognized by a person of ordinary skill in the art that "the DD is necessary and sufficient for apoptosis induction, at least when overexpressed in mammalian cells." (NX-2064, ¶ 21).

C. <u>**Dr. Reed's Publications Refute His Declaration Testimony On Critical Issues**</u>

272. Dr. Reed did not acknowledge in paragraph 21 that by March 17, 1997, a person of ordinary skill in the art would also have understood that the mere presence of a death domain structure in a protein does not reveal the function or activity of the molecule, and in particular, does not reveal that the molecule will induce apoptosis upon ligand binding, or even play a role in apoptosis because by that time it had been shown, for example, that several death domain-containing proteins were not implicated in cell-death induction. (*See,* AX-1086, ¶ 113 and NX-2064, ¶ 21).

273. Various publications written by Dr. Reed are contrary to the testimony he has provided in his expert declaration on this point. (AX-1095 and AX-1096).

274. Dr. Reed did not cite either AX-1095 and AX-1096 in his declaration.

275. For example, in the publication entitled "Apoptosis Database" Dr. Reed states the

following:

> The apoptotic domains maintained in the current version of the database are listed in Table 2. Of the 13 domains, 12 have representative structures in the PDB. The first three – death effector domain (DED), Caspase recruitment domain (CARD), and death domains (DDs) – share the same SCOP superfamily and fold. *Although the domains may be in several proteins involved in apoptosis, the mere presence of the domain does not guarantee an apoptotic function.* Nine of the 13 domains are also found in proteins that do not have direct involvement in apoptosis, as indicated by their Swiss-Prot annotation *Thus, the presence of a domain cannot be used to automatically define a protein's involvement in apoptosis.* [AX-1095, p. 622, col. 2, ¶ 1; Emphasis added].

276. In Table 2 of the "Apoptosis Database" article, Dr. Reed expressly states that a death domain does not have an exclusively apoptotic activity and that it is present in a wide variety of proteins. (AX-1095, p. 623, Table 2).

277. In his publication entitled "The Domains of Apoptosis: A Genomics Perspective" Dr. Reed states the following:

> *DD are not always involved in caspase activation, and some DDs indirectly suppress apoptosis through effects on NF-κB*, a family of transcription factors that have important roles in host defense and cell survival [reviewed in (22, 114)]. For example, the RIP protein binds TRADD and activates kinases that induce degradation of IκB, thus releasing NF-κB so that it can translocate to the nucleus and function as a transcription factor (115-117). Several antiapoptotic genes are among those induced by NF-κB, including the Caspase-8 antagonist FLIP, as well as certain members of the IAP family and Bcl-2 family (118-123). *The dual function of TRADD, as a partner for both caspase-activator FADD and NF-κB activator RIP, causes many of the TNF family receptors to counteract their own apoptosis-inducing activity. Thus, TNFR1, DR3, and DR6 are uncertain inducers of apoptosis unless NF-κB induction is inhibited,* in which case they typically elicit robust apoptotic responses (124, 125). In contrast, Fas and Trail Receptors DR4 and DR5 only rarely activate NF-κB, probably because these receptor complexes contain FADD but not TRADD (108, 109, 126, 127). [AX-1096, p. 10, col. 2, ¶ 1, Emphasis added; AX-1092, p. 1417, col. 2, ¶ 3].

D. Dr. Karin Disagrees with Many of Dr. Reed's Statements

278. Dr. Karin disagrees with Dr. Reed's statements that the '846 application provides an accurate description of a method for identifying antibodies that act as an agonist or antagonist

of a DR5. (AX-1086, ¶ 82 and NX-2064, ¶¶ 43-44).

279. The screening assays described in the '846 application (and discussed by Dr. Reed in paragraphs 43 through 45 of his Declaration) and in the references that Dr. Reed relies upon only discuss the general observation of cytotoxicity in response to a biological agent. (AX-1086, ¶ 82; AX-1037; and NX-2064, ¶¶ 43-45).

280. The screening assays and the references that Dr. Reed relies upon do not provide an accurate assessment of whether any observable morphological changes in cells are in fact the result of apoptosis-induction by an antibody acting in the same manner as when a cognate ligand binds to a DR5. (AX-1086, ¶ 82; AX-1037; and NX-2064).

281. Dr. Karin disagrees with Dr. Reed's suggestion in paragraph 43 of his Declaration that a person of ordinary skill in the art, by March 17, 1997, would have understood that the mere addition of an antibody to a cell culture containing DR5-transfected cells which resulted in an increase in the extent of apoptosis relative to that observed in a control experiment where no antibody was added meant that the antibody being added was an agonist of a DR5. (AX-1086, ¶ 93 and NX-2064, ¶ 43).

282. Instead, the lack of any information in the '846 application correlating apoptosis or any other cellular response to a cognate ligand binding to a DR5 would have precluded a person of ordinary skill in the art from doing so. (AX-1086, ¶ 93 and AX-1037).

283. Dr. Karin observed that Dr. Reed has suggested, at paragraph 25 of his Declaration, that conducting an overexpression assay in the absence of cognate ligand to the receptor is the preferred method to demonstrate apoptosis-inducing activity of "DD-containing TNFR-family members." (AX-1086, ¶ 95 and NX-2064, ¶ 25).

284. Dr. Reed also observes that performing this type of experiment would have been a

matter of routine experimentation for a person of ordinary skill in the art on March 17, 1997. (AX-1086, ¶ 95 and NX-2064).

285. Initially, Dr. Karin notes that the '846 application does not contain any information that establishes that a DR5 overexpression assay of this type was actually conducted. (AX-1086, ¶ 95 and AX-1037).

286. Dr. Karin could not find any results of such an assay in the '846 application. For the reasons discussed above, however, Dr. Karin does not agree with Dr. Reed that such an assay, standing alone, would have been the preferred method for demonstrating the apoptosis inducing activity of a new, previously uncharacterized death domain containing TNFR. (AX-1086, ¶ 95; NX-2064, ¶ 25; and AX-1037).

287. Dr. Reed then states at paragraph 24 of his Declaration that "induction of apoptosis involves aggregation of death receptors in the cell membrane, which leads to activation of a family of intracellular proteases ("caspases")." (AX-1086, ¶ 96 and NX-2064, ¶ 24).

288. Dr. Reed then suggests that it was known to a person of ordinary skill in the art by March 17, 1997, that "such aggregation could be caused by (i) ligand binding to the death receptor, (ii) antibody binding to the death receptor, or (iii) merely overexpressing the death receptor to cause aggregation." (AX-1086, ¶ 96 and NX-2064, ¶ 24).

289. Dr. Karin notes that Dr. Reed's observations have little relevance to the issues raised in this proceeding. The antibodies that are the subject of the Counts are defined by their capacity to (i) bind to an extracellular domain of a DR5, and (ii) either act, similar to cognate ligand activation, as an agonist or as an antagonist of the interaction of a DR5 with a cognate ligand. (AX-1086, ¶ 97)

290. Dr. Karin notes that Dr. Reed suggests that the '846 application describes the

antibodies of Count 1 and Count 2 because the application discloses the amino acid sequence of the receptor, certain predicted functions of the receptor, and general methods of preparing and screening antibodies. (AX-1086, ¶ 102 (Dr. Karin disagrees with Dr. Reed's assertions) and NX-2064, ¶¶ 45, 47).

291. Dr. Karin notes that Dr. Reed does not state in his declaration that, for example, that TNFα binding to TNFR1 activates the NF-κB pathway, which can operate to inhibit apoptosis in the cells expressing TNFR1. *See*, AX-1086, ¶ 98; AX-1046, Abstract ("…while activation of NF-κB protects against TNF-induced apoptosis)"; AX-1070, p. 784, col. 1, ¶ 1 ("However, a dose-dependant increase in cell survival was seen when RelA [NF-κB] was provided, with virtually complete protection at the highest dose (Fig. 3)"); AX-1071, Abstract ("[t]hese findings suggest that a negative feedback mechanism results from TNFα signaling in which NF-κB activation suppresses the signals of cell death"); and AX-1072, Abstract ("[t]he activation of the transcription factor …NF-κB by tumor necrosis factor (TNF) …was found to protect from cell killing.").

292. These examples of published literature demonstrated prior to March 17, 1997 that TNFR1 activation in many cell types promotes cell survival, not apoptosis, when it binds to its cognate ligand, TNFα. (AX-1086, ¶ 98).

293. Dr. Karin notes that Dr. Reed's statements in paragraph 24 of his Declaration present an incomplete and inaccurate picture as to what would have been well known to a person of ordinary skill in the art as of March 17, 1997. (AX-1086, ¶ 98 and NX-2064, ¶ 24).

294. Dr. Karin notes that at paragraph 20 of his Declaration, Dr. Reed states that a "death receptor" is a TNFR that contains a death domain. By March 17, 1997, it had been shown that TNFR1, Fas, DR3, and p75 NGFR each contained intracellular death domain structures. *See*,

AX-1086, ¶ 114; NX-2078; NX-2066, Results Summary ("...Apo-3 resembles TNFR1 and CD95 [Fas] in that it contains a cytoplasmic death domain"); and AX-1069, p. 216, col. 2, Results ("Comparisons of NTR with TNFR-1 and Fas intracellular domains detected matches in the previously-identified death domain at approximately 27% sequence identity.").

295. Dr. Karin notes that applying the rationale used in Dr. Reed's Declaration, the "death receptors" known by March 17, 1997, would include at least TNFR1, Fas, DR3 and p75 NGFR. Nonetheless, Dr. Reed only lists TNFR1, Fas and DR3 as the known death receptors as of March 17, 1997. (AX-1086, ¶ 114 and NX-2064, ¶ 20).

296. Dr. Karin disagrees with Dr. Reed's attempt to characterize the TNFR1, Fas, and DR3 receptors as receptors whose primary or sole function is to induce apoptosis upon binding by a cognate ligand. (AX-1086, ¶ 115).

297. For example, the primary function of TNFR1 was known to be the induction of inflammation which is considered as an opposite response to apoptosis. (AX-1086, ¶ 115).

298. Dr. Karin notes that Dr. Reed in his declaration acknowledges that NGFR (p75 NTR) is a receptor in the TNFR family, but he fails to acknowledge that it is a death domain-containing receptor. (AX-1086, ¶ 122 and NX-2064, ¶ 17).

299. Dr. Karin notes that Dr. Reed makes no observations on the degree of sequence identity or similarity between p75 NGFR and DR3, Fas or TNFR1. (AX-1086, ¶ 122 and NX-2064, ¶ 17).

300. Dr. Karin notes that Dr. Reed also does not discuss the biological effects induced by ligand binding to p75 NGFR that had been reported in the scientific literature by March 17, 1997. (AX-1086, ¶ 122 and NX-2064, ¶ 17).

301. Despite the fact that the degree of sequence identity or similarity of p75 NGFR to

TNFR1, Fas and DR3 may be within the same range as DR5 and these three TNFR family members, neither the '846 application nor Dr. Reed discuss p75 NGFR. (AX-1086, ¶ 123).

302. NGFR is an example of a TNFR family member with a death domain that does not induce apoptosis upon ligand binding and contradicts Dr. Reed's conclusions regarding the correlation of sequence identity or similarity and receptor function. (AX-1086, ¶ 123; AX-1037; and NX-2064).

303. Dr. Karin notes that Dr. Reed reports at paragraph 30 of his Declaration that the cysteine rich domains (CRD) of the DR5 sequence reported in the '846 application share about 22.4% homology to Fas, 30% homology to TNFR1 and 34.5% homology to DR3. (AX-1086, ¶ 128 and NX-2064, ¶ 30).

304. Dr. Karin notes that Dr. Reed notes in paragraph 31 of his Declaration that the death domain in the DR5 sequence reported in the '846 application shares 21.1% sequence identity with the death domain in Fas, 32.1% sequence identity to the death domain in TNFR1 and 32.8% sequence identity to the death domain in DR3. (AX-1086, ¶ 129 and NX-2064, ¶ 31).

E. Dr. Karin Disagrees With How Dr. Reed Characterized The *Wands* Factors

305. In general, Dr. Karin disagrees with how Dr. Reed characterized most of the criteria discussed in paragraph 35 of Dr. Reed's Declaration. (AX-1086, ¶ 134 and NX-2064, ¶ 35).

1. Nature of the Invention

306. At ¶ 35(a) of his Declaration, Dr. Reed characterizes the nature of the invention as "monoclonal antibodies." (AX-1086, ¶ 135 and NX-2064, ¶ 35(a)).

307. Dr. Reed does not, however, address important aspects of the monoclonal antibodies recited by Counts 1 and 2 (and Proposed Counts 3 and 4). For example, Dr. Reed does

not address the fact that the antigen to which the antibodies bind is a member of the TNFR family, a family of pleiotropic receptors. (AX-1086, ¶ 135 and NX-2064, ¶ 35(a)).

308. Dr. Reed does not address the fact that the monoclonal antibodies are required to exhibit a specific functional trait, agonism or antagonism, of a DR5. (AX-1086, ¶ 135 and NX-2064, ¶ 35(a)).

309. Dr. Karin believes that both of these aspects of the claimed monoclonal antibodies that Dr. Reed's testimony ignored - TNFR family antigen and functionality - raise significant questions that would have to be addressed experimentally before a person of ordinary skill in the art could have made or used such antibodies in March 17, 1997. (AX-1086, ¶ 135 and NX-2064, ¶ 35(a)).

2. *State Of The Prior Knowledge.*

310. At ¶ 35(b) of his Declaration, Dr. Reed relies on the fact that agonist and antagonist antibodies to Fas and TNFR1 had been made prior to March 17, 1997. Based on that knowledge, Dr. Reed assumes that a person of ordinary skill in the art in March 17, 1997 could have made agonist and antagonist antibodies to a new and uncharacterized and structurally distinct TNFR family member (*i.e.*, DR5). (AX-1086, ¶ 136 and NX-2064, ¶ 35(b)).

311. Dr. Karin does not believe that a person of ordinary skill in the art would have made such an assumption. It is Dr. Karin's opinion that the demonstration of production of antibodies that act as agonist or antagonists to other TNFR family members would not provide any particular guidance or insight into the task of producing a monoclonal antibody that acts as an agonist or an antagonist to a new, previously uncharacterized TNFR family member, such as DR5. (AX-1086, ¶ 136 and NX-2064, ¶ 35(b)).

3. *The Level Of Ordinary Skill.*

312. Regarding ¶35(c) of Dr. Reed's Declaration, as stated in Section II above, Dr. Karin believes that a person of ordinary skill in the field of TNF receptor research as of March 17, 1997, would have held an advanced degree in molecular biology or similar discipline or would have had significant laboratory experience and knowledge of the literature. As such, Dr. Karin believes that the level of ordinary skill in this field would have been high as of March 17, 1997. (AX-1086, ¶ 137 and NX-2064, ¶ 35(c)).

313. Dr. Karin does not believe that such a person would make sweeping assumptions about the structure-function relationship of a purported new member of the TNFR family or would have ignored state-of-the-art teachings regarding the diverse activities of members of the TNFR family. (AX-1086, ¶ 137 and NX-2064, ¶ 35(c)).

314. Instead, a person of ordinary skill in the art would have known that TNFR family members exhibit a very diverse range of characteristic biological effects when bound by their respective cognate ligands, and that such effects were generally unpredictable in the absence of some type of testing to determine a biological effect. (AX-1086, ¶ 137 and NX-2064, ¶ 35(c)).

4. *Level Of Predictability In The Field.*

315. Contrary to Dr. Reed's opinion at ¶35(d) of his Declaration, Dr. Karin believes the level of predictability in this field would have been very low as of March 17, 1997. (AX-1086, ¶ 138 and NX-2064, ¶ 35(d)).

316. As the '846 application itself acknowledges, TNFR and TNF ligand family members are very pleiotropic. (AX-1086, ¶ 138 and AX-1037, p. 3, lns. 15 to 17 and p. 26, lns. 19 to 22).

317. The pleiotropic nature of TNFR and TNF ligand family members adds a particular

level of uncertainty that is relevant to this proceeding; namely, an antibody that will induce a particular functional result when it binds to a DR5. Dr. Karin therefore disagrees with Dr. Reed's conclusion to the contrary. (AX-1086, ¶ 138 and NX-2064, ¶ 35(d)).

5. The Amount Of Direction Provided By The '846 Application.

318. Regarding the statements in ¶35(e) of Dr. Reed's Declaration, as a scientist, Dr. Karin does not consider the disclosure of the '846 application to provide a "substantial" amount of direction. (AX-1086, ¶ 139 and NX-2064, ¶ 35(d)).

319. For the reasons explained above, the identification of nucleotide and the deduced amino acid sequences of DR5, postulating the location of a putative extracellular domain and death domain, and the sequence alignment of DR5 to other members of the TNFR family would not have provided enough information to have enabled a person of ordinary skill in the art to predict what, if any, biological effects would be exhibited by cognate ligand binding to a DR5. (AX-1086, ¶ 139).

320. In fact, a person of ordinary skill in the art would have recognized that the '846 application did not even identify a cognate ligand of a DR5. (AX-1086, ¶ 139).

321. Instead, the '846 application leaves to others the substantial challenge of identifying a cognate ligand of a DR5, and then deciphering the biological effects associated with binding of that cognate ligand to a DR5. (AX-1086, ¶ 139 and AX-1037).

322. Dr. Reed observed that a cognate ligand to DR3 was not discovered until long after the DR3 receptor had been identified and classified as a member of the TNFR family. (AX-1086, ¶ 139 and NX-2064, ¶ 18).

323. Knowledge of the identity of a cognate ligand of a DR5 is essential to identify and characterize isolated antibodies that bind to a DR5 receptor and act as an agonist, an antagonist, or

neither an agonist or an antagonist. (AX-1086, ¶ 139).

324. A person of ordinary skill in the art would have also recognized that the '846 application fails to include any experimental demonstration of biological effects associated with ligand binding, which a person of ordinary skill in the art would have considered necessary to make and identify isolated agonist and/or antagonist antibodies. (AX-1086, ¶ 139 and AX-1037).

6. The Existence Of Working Examples.

325. In reference to ¶ 35(e) of Dr. Reed's Declaration, it should be noted that the '846 application provides no working examples regarding a DR5, let alone any particular monoclonal or other antibody that binds to an extracellular domain of the receptor and acts as an agonist or as an antagonist of a DR5. (AX-1086, ¶ 140 and NX-2064, ¶ 35(e)).

326. For example, a person of ordinary skill in the art would have recognized that the '846 application fails to disclose actual experimental data regarding: 1) the expression of DR5, 2) a function of DR5, 3) the identity of a cognate ligand to a DR5, or 4) the production of an antibody, let alone an agonist or antagonist antibody, of DR5. (AX-1086, ¶ 140 and AX-1037).

327. A person of ordinary skill in the art would have understood that actual experimental data would be necessary to describe subject matter involving considerable unpredictability. (AX-1086, ¶ 140).

328. The identification of an antibody that induces or inhibits unidentified biological effects through an unknown and uncharacterized cellular mechanism would have been, to a person of ordinary skill in the art, a very unpredictable undertaking. (AX-1086, ¶ 140).

329. A person of ordinary skill in the art would have considered the absence of a working example of an antibody to have been a significant omission of the '846 disclosure. (AX-1086, ¶ 140 and AX-1037).

7. *Quantity Of Experimentation Needed To Make And Use The Invention.*

330. In ¶ 35(g) of his Declaration, the only experimentation Dr. Reed mentions is the need for a person of ordinary skill in the art to "screen a number of antibodies to identify agonistic and antagonistic monoclonal antibodies to bind to the ECD of DR5." (AX-1086, ¶ 141 and NX-2064, ¶ 35(g)).

331. First, Dr. Karin disagrees that screening would have been the only experimentation necessary in order to identify agonist and antagonist antibodies of a DR5. For example, as explained above, without understanding the function of DR5 upon binding by a cognate ligand, the terms agonist and antagonist could not have been appropriately assigned to any antibody binding to a DR5 and exhibiting a particular characteristic. (AX-1086, ¶ 141).

332. Second, even if screening was the only work that needed to the conducted, which Dr. Karin does not believe to be true, Dr. Karin does not agree that such testing necessarily would have been routine. For example, the '846 application does not identify the parameters of any assay that could be used to identify and select isolated antibodies that act as agonists or as antagonists of a DR5. (AX-1086, ¶ 141 and AX-1037).

X. CONCLUSIONS

333. A person of ordinary skill in the art would not have concluded that the disclosure of the '846 or the '021 applications describe an isolated antibody that (i) binds to an extracellular domain of a DR5 and (ii) acts as an agonist or antagonist of a DR5. (AX-1086, ¶ 146; AX-1036; and AX-1037).

334. A person of ordinary skill in the art, equipped with the disclosure of either the '846 or the '021 application, could not have produced an isolated antibody that binds to an extracellular domain of a DR5 and acts as an agonist or antagonist of a DR5, without having to

engage in an undue amount of experimentation. (AX-1086, ¶ 147; AX-1036; and AX-1037).

CERTIFICATE OF FILING

The undersigned certifies that a copy of the paper entitled "**ADAMS OPPOSITION 3**" and its Appendices A-B were filed this 22nd day of February, 2006, by Federal Express overnight delivery service, to:

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The undersigned hereby certifies that a copy of the paper entitled "**ADAMS OPPOSITION 3**" and its Appendices A-B were served this 22nd day of February, 2006, by Federal Express overnight delivery service, on the Attorney of Record for the party Ni:

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EXHIBIT D

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Richard E. Schafer)

Human Genome Sciences, Inc.
Junior Party
(Patent 6,872,568;
Inventors: Jian Ni, Reiner L. Gentz, Guo-Liang Yu, Craig A. Rosen),

v.

Genentech, Inc.
Senior Party
(Application 10/423,448;
Inventors: Camellia W. Adams, Avi J. Ashkenazi, Anan Chuntharapai, Kyung Jin Kim).

Patent Interference No. 105,361 (RES)

NI REPLY 3

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I. The Evidence

The evidence cited for the first time in support of this Reply is set forth as Appendix A to this Reply.

II. Statement Regarding Adams' Material Facts

A concise statement admitting, denying, or stating that Party Ni is unable to admit or deny the material facts listed in Adams Opposition 3 is set forth as Appendix B to this Reply.

III. Ni Statement of Additional Material Facts

A statement of additional material facts in support of this Reply is set forth as Appendix C to this Reply.

IV. Argument

A. Overview

Party Adams ("Adams") has challenged Party Ni's ("Ni") request for benefit on the ground that Ni's 60/040,846 priority application ("the '846 application") allegedly fails to satisfy the written description and enablement requirements. (Material Facts ("MF") 335-342). The principal questions to be addressed by the Board in regards to Adams' opposition are: (a) whether disclosing a fully characterized DR5 and its extracellular domain ("ECD") is sufficient to describe agonistic and antagonistic antibodies of the counts; (b) whether a person of ordinary skill in the art would have believed the assertion in Ni's '846 application that activation of DR5 induces apoptosis; and (c) whether the '846 application would have enabled one of ordinary skill in the art to identify agonistic and antagonistic antibodies of the counts. As explained in Ni's Substantive Motion 3 and highlighted below, each of these questions should be answered in the affirmative and Ni should be accorded benefit of its priority applications including the '846 application.

B. Adams Has Provided No Basis for Challenging Dr. Reed's Testimony

At p.25:5-10 of the opposition, Adams instructs the Board to "carefully scrutinize" Dr. Reed's testimony and "accord it little weight," based on statements made by a district court in an unrelated proceeding. (MF 343-345).

Ni's response is: The Board cannot properly draw any negative inferences as to Dr. Reed's credibility or the weight to which his testimony should be accorded, based on statements by a non-controlling district court in a completely unrelated proceeding that did not relate to patents or interference-related issues. (MF 346). Since Adams chose not to cross-examine Dr. Reed (MF 347-348), Adams has no basis for challenging Dr. Reed's credibility, the validity of his conclusions or the evidence that was considered by Dr. Reed in rendering his opinion.

At p.4:8-17 of the opposition, Adams' asserts that Dr. Reed's testimony regarding the ability to predict apoptotic activity based on the presence of a death domain in a TNFR "directly conflicts" with statements in Dr. Reed's own publications. (MF 349-351, 354).

Ni's response is: Dr. Reed's publications, cited by Adams, do not state or imply that death domain-containing TNFRs do not induce apoptosis. (MF 352-353, 355). Thus, Dr. Reed's testimony does not conflict with his publications. This is one of many examples in which Adams is, at best, confused by the scientific evidence, or at worst, intentionally trying to mislead the Board by citing to evidence that does not support its argument.

At p.14:24-25 of the opposition, and at ¶¶ 114, 122-124 of Dr. Karin's Declaration, Adams and Dr. Karin also suggest that Dr. Reed intentionally and improperly omitted p75 NGFR ("NGFR") and CD40 from the list of apoptosis-inducing death receptors set forth at paragraph 20 of Dr. Reed's Declaration. (MF 356-359).

Ni's response is: Dr. Karin confirmed on cross-examination that the predominant view in the art as of March 1997 was that NGFR and CD40 were *not* considered death receptors. (MF 360-384). In fact, as admitted by Dr. Karin, several authors -- including himself and scientists from Genentech -- published scientific articles in 1997 identifying the same three molecules (Fas, TNFR1 and DR3) that are described in Dr. Reed's declaration as the only then-known death receptors. (MF 360-384). Dr. Karin also admitted that none of these references, including his own, classified NGFR or CD40 as death receptors. (MF 360-384). Thus, it was appropriate and scientifically accurate for Dr. Reed to omit NGFR and CD40 from the list of death receptors in his declaration. Moreover, it was disingenuous for Adams and Dr. Karin to challenge Dr. Reed's credibility on this point when the prevailing view in the art (including their own) was that these molecules were not death receptors. Ironically, Dr. Karin, himself, failed to cite several highly relevant papers in his own declaration that contradict his testimony. (MF 542-545).

Significantly, Adams' attack on Dr. Reed's credibility is inconsistent with the fact that Genentech recently asked Dr. Reed to write a letter of recommendation for one of the inventors on the Adams' application (Avi J. Ashkenazi). (MF 386). Certainly, in determining whether to promote one of its scientists, Genentech would not rely on the opinion of someone whose opinion should be accorded "little weight."

C. The Federal Circuit's Decision in Noelle *Supports Ni's Request for Benefit*

The Federal Circuit confirmed in *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004), that disclosure of a fully characterized antigen will satisfy the written description requirement for antibodies specific to that antigen. At p.20:12-17 of the opposition, Adams argued that *Noelle* does not apply and that disclosing a DR5 antigen is not sufficient to provide written description for antibodies of the counts. (MF 392-396).

Ni's response is: The circumstances of the present interference fall squarely within the situation addressed in *Noelle*. In *Noelle*, the claims were directed to monoclonal antibodies specific for a human CD40CR antigen. *Id.*, 355 F.3d at 1346, 69 USPQ2d at 1511. The court confirmed that Noelle could have adequately described such antibodies by disclosing a fully characterized antigen, *Id.*, 355 F.3d at 1349, 69 USPQ2d at 1514, even though one would have had to screen for such antibodies. In the present case, as in *Noelle*, a fully characterized antigen (the DR5 ECD) is described, and only routine screening would have been needed to obtain and identify antagonistic and agonistic DR5 antibodies. (MF 33-42). In fact, both Dr. Karin and Dr. Reed agree that such screening would have been routine. (MF 470-472). Thus, under *Noelle*, disclosing a fully characterized DR5 ECD is sufficient to describe the antibodies of the counts.

Adams has not provided a satisfactory explanation as to why *Noelle -- the Federal Circuit's most recent and most pertinent decision on written description for antibodies* -- should not apply. Rather, Adams, <u>at p.17:24 - p.19:17 of the opposition</u>, has cited to *Fiers v. Revel* and *University of Rochester v. G.D. Searle* to support its position that one must disclose the structure of an antibody or provide a biological deposit to satisfy the written description requirement.

Ni's response is: *Fiers* and *University of Rochester* dealt with distinct circumstances and technical subject matter; neither case involved antibodies. Antibodies are fundamentally different from unknown nucleic acids (*Fiers*) and unknown compounds that interfere with enzymatic activity (*University of Rochester*). Antibodies are commonly defined in terms of the antigen to which they bind. In view of the unique properties of antibodies, the Federal Circuit confirmed *in Noelle* that a fully characterized antigen is sufficient to adequately describe antibodies to the antigen, even though routine screening may be needed to obtain such antibodies.

Adams' assertion that one must describe the structure of an actual antibody (*e.g.*, by sequence or by epitope specificity), or provide a biological deposit, to satisfy the written description requirement is not only contrary to the existing state of the law, but is also illogical from a scientific point of view. Dr. Karin confirmed on cross-examination that the amino acid sequence of an antibody provides information about only *that particular antibody* or an isotype thereof and does not provide a description of an entire class of antibodies. (MF 397-398). In addition, by March 1997, it was known that death receptor-specific antibodies induced apoptosis through receptor aggregation, and therefore apoptosis induction is epitope-independent; *e.g.*, antibodies that promote receptor aggregation were deemed agonists of the receptors. (MF 399-406). These observations contradict Adams' and Dr. Karin's assertion that an epitope can describe an antibody with a particular function. To describe agonistic or an antagonistic antibodies, it was appreciated that function is more important than structure. In Dr. Karin's words, "if people want to know whether an antibody induces apoptosis they just test it." (MF 398). Indeed, this is all that *Noelle* requires.

Finally, Adams' assertion that one must describe the structure of an actual antibody or provide a biological deposit to satisfy the written description requirement contradicts arguments previously made by Genentech before the USPTO to obtain allowance of claims to agonistic antibodies. (MF 413-425). If accepted, Adams' theory would also render unpatentable broad claims to agonistic and antagonistic antibodies as set forth in several of Genentech's pending applications and granted patents. (MF 407-412).

D. Adams' Definition of Agonistic and Antagonistic Antibodies Is Not Controlling

At p.16:22-23 of the opposition, Adams has challenged Ni's request for benefit on the ground that the '846 application allegedly does not identify a "cognate ligand" for DR5 or the

biological effect of cognate ligand binding to a DR5. (MF 426). For this argument, Adams relies on Dr. Karin's narrow and arbitrary definition of agonists and antagonists which requires knowledge of the biological effects of cognate ligand binding to the receptor. (MF 427-431).

Ni's response is: Dr. Karin's definition of agonists and antagonists is not controlling in this interference. Dr. Karin admitted on cross-examination that, contrary to his asserted definition, several technical sources define agonists and antagonists without reference to a cognate ligand or to the biological effects of cognate ligand binding. (MF 434-451). Dr. Karin also admitted that several scientific references published prior to March 1997 (including Genentech's own publications) characterize antibodies against various receptors as "agonists" or "antagonists" without knowing the ligand. (MF 452-469). Dr. Karin admittedly did not consider sources besides Goodman and Gilman's to define agonists and antagonists, (MF 432-433), even though he admitted that there are multiple definitions for these terms. (MF 451).

In count construction, when there are multiple accepted definitions of a term, it is improper to rely on a single definition advanced by a party's expert simply because it is the definition most familiar to that expert; rather, the parties' specifications should be consulted. *Adang v. Fischhoff*, 286 F.3d 1346, 1353, 62 USPQ2d 1504, 1509 (Fed. Cir. 2002). Neither Ni's involved patent nor Adams' involved application define antagonists or agonists in terms of cognate ligand binding. (MF 473-476). To the contrary, both disclosures are consistent with definitions of agonists and antagonists that relate to whether apoptosis is enhanced or inhibited. (MF 473-476). The definition advanced by Adams and Dr. Karin ignores the parties' disclosures and other competing definitions and is therefore not controlling.

Nonetheless, Adams' and Dr. Karin's definition of agonistic and antagonistic antibodies *is* an admission against interest. In this regard, Dr. Karin admitted on cross-examination that none

of the Examples in Adams' '119 application show a reduction to practice of an agonistic or an antagonistic antibody under Dr. Karin's definition. (MF 477-498). Thus, by asserting and relying on Dr. Karin's definition, Adams has admitted that Adams' '119 application is not a constructive reduction to practice of the subject matter of the counts.

E. Ni's '846 Application Sufficiently Predicts an Apoptotic Function for DR5

At p.11:9-13 of the opposition, Adams asserts that a person of ordinary skill in the art would not have believed that activation of DR5 would induce apoptosis because, according to Adams, the TNFR superfamily was "recognized as having diverse biological functions." (MF 499).

Ni's response is: The '846 application does not merely identify DR5 as a member of the TNFR superfamily; rather, the '846 application identifies DR5 as a death domain-containing TNFR -- *i.e.*, a *death receptor* -- and specifically compares DR5 to the known death receptors Fas, TNFR1 and DR3. (MF 500-505, 22). Thus, Adams' assertion of the alleged "diverse biological functions" of TNFRs in general is irrelevant to the issue of whether a person of ordinary skill in the art would have reasonably believed that DR5, a death receptor, would induce apoptosis. Since all of the known death domain-containing TNFRs in March 1997 (Fas, TNFR1 and DR3) were known to induce apoptosis (MF 506-509), a person of ordinary skill in the art would have reasonably believed that DR5 would also induce apoptosis.

At p.14:14-23 of the opposition Adams asserts that death domain-containing *proteins* were known in the art in March 1997 that allegedly were not implicated in apoptosis; Adams cites to ¶¶ 112 and 113 of Dr. Karin's Declaration to support this assertion. (MF 510, 512, 513).

Ni's response is: This is another attempt by Adams to mislead the Board. Dr. Karin admitted that the "proteins" cited at ¶¶ 112 and 113 of his declaration are *not* TNFRs. (MF 514).

DR5 is identified in the '846 application, not just as a death domain-containing *protein*, but as a death domain-containing *TNFR*. Since all death domain-containing TNFRs were known to induce apoptosis by March 1997 (MF 506-509), the results allegedly observed with *non-TNFR* death domain containing *proteins* are irrelevant to whether a person of ordinary skill in the art would have reasonably believed that activation of DR5 induces apoptosis.

At p.15:7-10 of the opposition, Adams asserts that TNFR1 and Fas had been shown to induce other activities, besides apoptosis, under certain conditions. (MF 511, 515-517).

Ni's response is: Once again, Adams is attempting to mislead the Board. It was well established by 1997 that TNFR1, Fas and DR3 induced apoptosis (MF 507-509, 519-527); Dr. Karin even admitted on cross-examination that the prevailing view in the art by March 1997 was that the "central role" of Fas was to trigger apoptosis. (MF 518). Thus, Adams has failed to establish that a person of ordinary skill in the art would have doubted that activation of DR5 would induce apoptosis in view of the prevailing views in the art in March 1997 that a central role of death domain containing TNFRs was apoptosis induction.

F. Ni's '846 Application Would Have Enabled One of Ordinary Skill in the Art to Identify Agonistic or Antagonistic Antibodies of the Counts

At p.15:22 - p.16:6 of the opposition, Adams, relying on Dr. Karin's declaration, asserted that the '846 application would not have enabled a person of ordinary skill in the art to identify agonistic and antagonistic antibodies of the counts because, according to Dr. Karin, the overexpression assay described in the '846 application could not have been used to screen for agonists or antagonists of DR5. (MF 528-529).

Ni's response is: This is another example where Dr. Karin's testimony on cross-examination directly conflicts with his declaration. On cross-examination, Dr. Karin admitted

that by March 1997, overexpressing death receptors in cells was widely used, even by Genentech, to mimic receptor activation. (MF 530-541). Dr. Karin also admitted that MCF7 cells, which are used in Example 5 of the '846 application to assess DR5's apoptotic activity, are "special" in that external measures to inactivate NF-κB activity are not needed to observe apoptosis in these cells. (MF 520-521). Thus, consistent with Dr. Reed's testimony, overexpressing DR5 in, *e.g.*, MCF7 cells, could have been used to identify agonistic and antagonistic antibodies against DR5. Adams' and Dr. Karin's arguments to the contrary are disingenuous in the face of the numerous examples, including Genentech's own publications and patents, in which overexpression assays were used to assess death receptor activation.

G. The Distinction Between Monoclonal and Polyclonal Antibodies is Irrelevant

Since constructive reduction to practice requires an enabled description of *only one embodiment* of the count, and since all of the counts, including Ni proposed counts 3 and 4, encompass monoclonal antibodies, Adams' assertions at p.24:5-7 of the opposition, regarding alleged "technical distinctions" between monoclonal and polyclonal antibodies are irrelevant to the benefit inquiry.

H. Dr. Karin's Testimony Should be Accorded Little or No Weight

Adams' opposition relies on the opinion of Dr. Karin as to what was allegedly known or believed by persons of ordinary skill in the art by March 1997. As indicated elsewhere herein, on many technical issues Dr. Karin's views stand in stark contrast to the prevailing views in the art. (*See*, *e.g.*, MF 357-385, 430-472, 529-541). On cross-examination, Dr. Karin expressed outright disagreement with the views and conclusions of several prominent scientists, many of whom Dr. Karin admitted were "experts in the field of apoptosis." (MF 360-385, 464, 467-468). Thus, Dr. Karin is an outlier, and his opinions should be accorded little weight by the Board.

Moreover, Dr. Karin apparently has significant personal interest in the outcome of these proceedings. For example, shortly after the interference was declared, Dr. Karin wrote a glowing letter of recommendation for Adams' inventor, Dr. Avi Ashkenazi. (MF 387-389). Dr. Karin's Declaration should have disclosed his relationship with Genentech because, as noted by the Board in a recent decision also involving Genentech, "such relationships may be vital when evaluating testimony regarding written description and should be disclosed in the declaration." *Scripps Res. Inst. v. Genentech, Inc.*, 77 USPQ2d 1809, 1815, n. 5 (BPAI 2005). Furthermore, Dr. Karin admitted that he owns approximately $80,000 worth of Genentech stock (and stated that he wished he owned ten times more). (MF 390-391).

In view of the foregoing, the Board should accord little or no weight to Dr. Karin's testimony, including his narrow and arbitrary construction of the terms "agonist" and "antagonist," except to the extent that his testimony constitutes an admission against Adams' interest. Finally, the Board is encouraged to view Dr. Karin's video deposition to observe his demeanor and his evasiveness in responding to many of the questions he was asked on cross-examination. (*See e.g.*, MF 546-552).

Accordingly, Adams Opposition 3 should be denied and Ni Substantive Motion 3 should be granted.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Jorge A. Goldstein, hereby certify that a copy of the foregoing NI REPLY 3, filed April 5, 2006, has been served on the attorney of record of Party Adams via Federal Express on this 5th day of April 2006, addressed as follows:

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Respectfully submitted,

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Date: April 5, 2006
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APPENDIX A: EVIDENCE CITED FOR THE FIRST TIME IN SUPPORT OF THE REPLY

The following evidence was not cited in Ni Substantive Motion 3 because it supports responses to issues and/or facts that were raised in the first instance in Adams Opposition 3. This evidence is not necessary to make out a *prima facie* case for the relief requested in Ni Substantive Motion 3.

Exhibit #	***Description***
Exhibit 2023	Pan *et al.*, *Science 276*:111-113 (April 4, 1997) "The Receptor for the Cytotoxic Ligand TRAIL"
Exhibit 2040	Declaration of Avi Ashkenazi under 37 C.F.R. §1.131 submitted to Examiner Kaufman at the PTO by Party Adams on January 22, 2003 in its Application No. 09/020,746, as an exhibit to its January 22,2003 Amendment and Supplemental Response
Exhibit 2116	Non-Provisional Application Transmittal for U.S. Appl. No. 08/857,215, filed on May 15, 1997
Exhibit 2117	U.S. Patent Appl. No. 08/857,216, filed January 16, 1996
Exhibit 2118	Non-Provisional Application Transmittal for U.S. Appl. No. 09/020,746
Exhibit 2119	Office Action issued on October 18, 2002 in U.S. Patent Appl. No. 09/020,746
Exhibit 2120	Amendment and Response to October 18, 2002 Office Action, dated October 21, 2002, filed in U.S. Patent Appl. No. 09/020,746
Exhibit 2121	Rule 131 Declaration signed by Avi Ashkenazi on October 15, 2002, filed in U.S. Appl. No. 09/020,746
Exhibit 2122	Rule 131 Declaration signed by Avi Ashkenazi on October 15, 2002, filed in U.S. Appl. No. 09/020,746
Exhibit 2125	Examiner's Amendment dated September 27, 2002, issued in U.S. Appl. No. 09/020,746
Exhibit 2127	Casaccia-Bonnefil et al., Nature 383: 716 (1996)
Exhibit 2128	Frade et al., Nature 383: 166 (1996)
Exhibit 2129	Carter et al., Neuron 18: 187-190 (1997)
Exhibit 2130	Lippincott's Illustrated Reviews: Pharmacology 2nd Edition p.20 (1997) (*See* NX2156 for supplemented exhibit)
Exhibit 2131	Stedman's Medical Dictionary 26th Edition p.38 (1995)
Exhibit 2132	Essentials of Pharmacology, 2nd ed., p. 4 (1996) (*See* NX2158 for supplemented exhibit).
Exhibit 2133	Basic Pharmacology p.15 (1996) (submitted at the deposition of March 20, 2006 as "Essentials of Pharmacology p. 15", *see* NX2143 and NX2157 for supplemented exhibits).
Exhibit 2134	Bennett et al., J. Biol. Chem. 269(19): 14211 (1994)

Exhibit #	*Description*
Exhibit 2135	Mark et al., J. Biol. Chem. 269(14): 10720 (1994)
Exhibit 2136	Uckun et al., J. Biol. Chem. 266(26): 17478 (1991)
Exhibit 2137	Armitage et al., Nature 357: 80 (1992)
Exhibit 2138	Ogasawara et al., Nature 364: 806 (1993)
Exhibit 2139	Suda et al., Cell 75: 1169 (1993)
Exhibit 2140	U.S. Application No. 60/072,481
Exhibit 2141	Casaccia-Bonnefil et al., Nature 383: 716 (1996)
Exhibit 2144	Walczak et al., EMBO J 16(17): 5386 (1997)
Exhibit 2145	MacFarlane et al., J. Biol. Chem. 272(41): 25417 (1997)
Exhibit 2146	Wu et al., Nature Genetics 17: 141 (1997)
Exhibit 2147	Herdegen et al., J Neuroscience 18(14): 5124 (1998)
Exhibit 2150	Letter dated November 10, 2005 from Dr. Michael Karin to Dr. Vishva Dixit
Exhibit 2151	Chuntharapai et al., J. Immunol. 166: 4891 (2001)
Exhibit 2152	U.S. Appl. No. 2003/0004313
Exhibit 2153	U.S. Patent No. 6,689,744
Exhibit 2154	U.S. Patent No. 5,910,574
Exhibit 2156	Lippincott's Illustrated Reviews: Pharmacology 2nd Edition, Chapter 2: Pharmacokinetics and Drug Receptors p. 17-26 (1997)
Exhibit 2157	Basic Pharmacology 4th Edition, Chapter 1: General Pharmacology p. 1-32 (1996)
Exhibit 2158	Essentials of Pharmacology 2nd Edition, Chapter 1: General Principles and Pharmacokinetics p.1-33 (1996)
Exhibit 2159	Mapara et al., Eur J Immunol 23: 702-708 (1993)
Exhibit 2160	Kitson et al., Nature 384: 372 (1996)
Exhibit 2161	Transcript of deposition of Dr. Michael Karin taken on March 21 and 22, 2006 (in two volumes, without errata sheets)
Exhibit 2162	Videotaped copy of deposition of Dr. Michael Karin taken on March 21 and 22, 2006 (six disks)
Exhibit 2163	Email from Vishva Dixit to John Reed, dated October 18, 2005
Exhibit 2164	Morningstar Historical Stock Prices for Genentech, January 2, 2002 through March 30, 2006 (http://quicktake.morningstar.com/stock, visited 3/31/06)

With regard to Exhibits 2161 and 2162 (the transcript and video copy of the deposition of Dr. Michael Karin, taken on March 21 and 22, 2006), Party Ni is submitting the entire transcript for completeness; however, Party Ni reserves the right to object to all or part of the redirect portion of

the deposition. In addition, Exhibit 2161 is being submitted without the signed Acknowledgement page or errata sheets since these documents have not been received by Party Ni.

APPENDIX B: STATEMENTS REGARDING PARTY ADAMS' MATERIAL FACTS

Although Ni denies several of Adams Facts, as indicated below, such facts may nonetheless be used as admissions against Adams's interests.

75. Party Ni admits Adams Fact 75.

76. Party Ni admits Adams Fact 76.

77. Party Ni admits Adams Fact 77 to the extent that Ni proposed count 3 is:

> An isolated antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2, wherein the antibody or fragment thereof is an antagonist of the protein of SEQ ID NO:2,
>
> Or
>
> Claim 134 of Adams Application 10/423,448.

78. Party Ni admits Adams Fact 78.

79. Party Ni admits Adams Fact 79 to the extent that Ni proposed count 4 is:

> An isolated antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2, wherein the antibody or fragment thereof is an agonist of the protein of SEQ ID NO:2,
>
> Or
>
> Claim 133 of Adams Application 10/423,448.

80. Party Ni admits Adams Fact 80.

81. Party Ni admits Adams Fact 81.

82. Party Ni admits Adams Fact 82.

83. Party Ni admits Adams Fact 83.

84. Party Ni is unable to admit or deny Adams Fact 84 because the asserted definition of a "person of ordinary skill in the art" is not a *fact* but rather an *opinion* of Dr. Karin. (Paragraph 39 of the Declaration of Dr. Karin, cited in support of Adams Fact 84 begins with "In my opinion . . .")

85. Party Ni admits Adams Fact 85 only to the extent that the asserted definition of "antibody" is the definition that is set forth in paragraph 41 of the Declaration of Dr. Karin. Ni does not admit that this is the only definition of an "antibody."

86. Party Ni admits Adams Fact 86.

87. Party Ni admits Adams Fact 87.

88. Party Ni admits Adams Fact 88.

89. Party Ni admits Adams Fact 89.

90. Party Ni admits Adams Fact 90 only to the extent that the referenced Figure (Fig. 3) is one possible illustration of the structure of an antibody of the IgG isotype.

91. Party Ni admits Adams Fact 91.

92. Party Ni admits Adams Fact 92.

93. Party Ni admits Adams Fact 93.

94. Party Ni admits Adams Fact 94.

95. Party Ni admits Adams Fact 95.

96. Party Ni admits Adams Fact 96 only to the extent that the asserted technical proposition is set forth at paragraph 51 of the Declaration of Dr. Karin.

97. Party Ni is unable to admit or deny Adams Fact 97 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

98. Party Ni admits Adams Fact 98.

99. Party Ni is unable to admit or deny Adams Fact 99 because the asserted statement ("Equipped with the discussed in paragraph 98, a particular binding specificity can be associated with a particular amino acid sequence and antibody structure.") is grammatically incorrect and it is unclear what is being asserted.

100. Party Ni is unable to admit or deny Adams Fact 100 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

101. Party Ni is unable to admit or deny Adams Fact 101 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

102. Party Ni is unable to admit or deny Adams Fact 102 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

103. Party Ni is unable to admit or deny Adams Fact 103 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

104. Party Ni is unable to admit or deny Adams Fact 104 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

105. Party Ni is unable to admit or deny Adams Fact 105 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

106. Party Ni is unable to admit or deny Adams Fact 106 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

107. Party Ni admits Adams Fact 107 only to the extent that Sevier *et al.*, *Clin. Chem. 27*:1797-1806 (1981) refers to "major immunodiagnostic advantages" of monoclonal antibodies compared to polyclonal antiserum.

108. Party Ni is unable to admit or deny Adams Fact 108 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by the cited evidence (Sevier *et al.*, *Clin. Chem. 27*:1797-1806 (1981) does not refer to "consistent biological effect" of monoclonal antibodies).

109. Party Ni is unable to admit or deny Adams Fact 109 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by the cited evidence (Sevier *et al.*, *Clin. Chem. 27*:1797-1806 (1981) does not refer to diverse "effector functions" of polyclonal antisera).

110. Party Ni is unable to admit or deny Adams Fact 110 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

111. Party Ni is unable to admit or deny Adams Fact 111 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

112. Party Ni admits Adams Fact 112 only to the extent that the asserted statement relates to *possible* signaling pathways associated with "cell surface receptors" in general.

113. Party Ni is unable to admit or deny Adams Fact 113 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

114. Party Ni admits Adams Fact 114.

115. Party Ni admits Adams Fact 115 only to the extent that inflammation, apoptosis, costimulation of T-cells and B-cells, tumor necrosis, JNK and NF-κB pathway activation, and cell proliferation are mentioned in the cited references.

116. Party Ni admits Adams Fact 116 and notes that the second quotation, taken from page 26, lines 5-8 of the '846 application, is in reference to "The Tumor Necrosis Factor (TNF) family ligands" and not to TNF receptors.

117. Party Ni is unable to admit or deny Adams Fact 117 because it is unclear what is meant by "undifferentiated interactions between TNF ligand family members and TNFR family members."

118. Party Ni is unable to admit or deny Adams Fact 118 because it is unclear what is meant by "one receptor/one ligand basis" and "more complex types of interactions."

119. Party Ni is unable to admit or deny Adams Fact 119 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

120. Party Ni is unable to admit or deny Adams Fact 120 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

121. Party Ni admits Adams Fact 121 only to the extent that (1) counts 1 and 2 recite "[a]n isolated monoclonal antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2," (2) counts 3 and 4 recite "[a]n isolated antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2," (3) counts 1 and 3 further recite "wherein said antibody or fragment thereof is an antagonist of the protein of SEQ ID NO:2," and (4) counts 2 and 4 further recite "wherein said antibody or fragment thereof is an agonist of the protein of SEQ ID NO:2."

122. Party Ni admits Adams Fact 122 only to the extent that counts 1 and 2 recite "[a]n isolated monoclonal antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2," and counts 3 and 4 recite "[a]n isolated antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2."

123. Party Ni is unable to admit or deny Adams Fact 123 because it is unclear what "This binding function" refers to. Moreover, Party Ni is unable to admit or deny Adams Fact 123 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

124. Party Ni admits Adams Fact 124 only to the extent that counts 1 and 3 recite "wherein said antibody or fragment thereof is an antagonist of the protein of SEQ ID NO:2," and counts 2

and 4 recite "wherein said antibody or fragment thereof is an agonist of the protein of SEQ ID NO:2."

125. Party Ni is unable to admit or deny Adams Fact 125 because it is unclear what "This requirement" refers to. Moreover, Party Ni is unable to admit or deny Adams Fact 125 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

126. Party Ni is unable to admit or deny Adams Fact 126 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

127. Party Ni admits Adams Fact 127 only to the extent that the block quotation is found in Goodman and Gilman's, The Pharmacological Basis of Therapeutics (Ninth Edition (1996), p. 29 bridging p. 30).

128. Party Ni admits Adams Fact 128 only to the extent that, by March 17, 1997, it was known in the art that TNFR family members participated in intracellular signaling functions.

129. Party Ni admits Adams Fact 129 only to the extent that the binding of a ligand to a TNFR family member can initiate intracellular signaling.

130. Party Ni is unable to admit or deny Adams Fact 130 because it is not clear what is meant by a "variety" of observable biological effects.

131. Party Ni admits Adams Fact 131 only to the extent that Eischen *et al.*, *Blood 90*:935-943 (1997) states that "treatment of wild-type Jurkat cells with anti-Fas or the topoisomerase II-directed agent etoposide resulted in proteolytic cleavage of precursors for the cysteine-

dependent aspartate-directed proteases caspase-3 and caspase-7 and degradation of the caspase substrates poly(ADP-ribose)polymerase (PARP) and lamin B_1;" and Chinnaiyan *et al. Science 247*:990-992 (1996) states that "[o]verexpression of CD95 and TNFR-1 in mammalian cells mimics receptor activation."

132. Party Ni is unable to admit or deny Adams Fact 132 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

133. Party Ni denies Adams Fact 133.

134. Party Ni denies Adams Fact 134.

135. Party Ni admits Adams Fact 135 only to the extent that disclosure of "portions of the variable domains of the light and heavy immunoglobulin chains that are necessary to define the epitope binding specificity of the antibody, or the sequence of a nucleic acid encoding such portions of the light and heavy chains" is one potential way in which a monoclonal antibody of count 1 or count 2 might be adequately described.

136. Party Ni admits Adams Fact 136 only to the extent that disclosure of "a hybridoma or other cell line that produces a representative DR5 antibody" is one potential way in which a monoclonal antibody of count 1 or count 2 might be adequately described.

137. Party Ni denies Adams Fact 137.

138. Party Ni denies Adams Fact 138.

139. Party Ni denies Adams Fact 139.

140. Party Ni admits Adams Fact 140 only to the extent that, as a person of ordinary skill in the art would fully appreciate, control experiments could have been easily conducted to ensure that agonistic and antagonistic antibodies against DR5 produced biological consequences that were not the result of "non-receptor interactions with the cell."

141. Party Ni admits Adams Fact 141 and notes that apoptosis caused by a DNA damaging agent could be easily distinguished from apoptosis caused by an agonistic DR5 antibody by performing routine control experiments.

142. Party Ni denies Adams Fact 142.

143. Party Ni denies Adams Fact 143.

144. Party Ni denies Adams Fact 144.

145. Party Ni denies Adams Fact 145.

146. Party Ni admits Adams Fact 146 only to the extent that the quoted language is found within the '846 Application.

147. Party Ni admits Adams Fact 147 only to the extent that Chu, *J. Biol. Chem. 269*:787-790 (1994) states that "The cytotoxicity of cisplatin is believed to be due to the formation of DNA adducts, which include DNA-protein cross-links, DNA monoadducts, and interstrand and intrastrand DNA cross-links," and that Prakash and Timasheff, *J. Biol. Chem. 258*:1689-1697 (1983) states that "Early morphological studies have shown that VCR destroys spindle microtubules . . . suggesting a specific interaction between VCR and the microtubule protein."

148. Party Ni denies Adams Fact 148.

149. Party Ni is unable to admit or deny Adams Fact 149 because it is unclear what is meant by "actual experimental characterization or testing," and it is noted that the '846 application provides a DR5 amino acid sequence and illustrates a sequence alignment between the DR5 amino acid sequence and that of Fas, TNFR-1 and DR3 (in the field of bioinformatics, for example, sequence alignments and analysis may be regarded as "actual experimental characterization or testing.")

150. Party Ni admits Adams Fact 150 only to the extent that an actual working example of DR5 polypeptide expression is not set forth in the '846 application.

151. Party Ni denies Adams Fact 151.

152. Party Ni admits Adams Fact 152.

153. Party Ni admits Adams Fact 153.

154. Party Ni denies Adams Fact 154.

155. Party Ni is unable to admit or deny Adams Fact 155 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

156. Party Ni admits Adams Fact 156.

157. Party Ni admits Adams Fact 157 only to the extent that an actual working example confirming that DR5 binds TRAIL is not set forth in the '846 application.

158. Party Ni admits Adams Fact 158 only to the extent that an actual working example confirming that DR5 induces apoptosis is not set forth in the '846 application, but a prophetic example (later confirmed by a working example in the '021 application) of DR5-induced apoptosis is set forth as Example 5 in the '846 application.

159. Party Ni denies Adams Fact 159.

160. Party Ni denies Adams Fact 160.

161. Party Ni denies Adams Fact 161.

162. Party Ni is unable to admit or deny Adams Fact 162 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

163. Party Ni denies Adams Fact 163.

Adams Fact 164 contains two independent parts.

164. Party Ni admits the *first part* of Adams Fact 164 only to the extent that an actual working example of DR5 overexpression is not set forth in the '846 application.

164. Party Ni is unable to admit or deny the *second part* of Adams Fact 164 because the asserted statement (*i.e.*, that "[a]n overexpression assay, standing alone, would not have been the preferred method for demonstrating the apoptosis inducing activity of a new, previously uncharacterized death domain containing TNFR") is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by the cited evidence.

165. Party Ni is unable to admit or deny Adams Fact 165 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

166. Party Ni admits Adams Fact 166 only to the extent that the cited evidence indicates that, under certain circumstances, TNFα binding to TNFR1 can activate the NF-κB pathway and inhibit apoptosis.

167. Party Ni denies Adams Fact 167.

168. Party Ni admits Adams Fact 168 only to the extent that an actual deposit of a hybridoma that produces an agonistic or antagonistic antibody against the DR5 extracellular domain is not mentioned in the '846 application.

169. Party Ni denies Adams Fact 169.

170. Party Ni denies Adams Fact 170.

171. Party Ni denies Adams Fact 171.

172. Party Ni denies Adams Fact 172.

173. Party Ni denies Adams Fact 173.

174. Party Ni admits Adams Fact 174 only to the extent that the '846 application does not identify any particular assay as a "control assay" because such controls would have been evident to one of ordinary skill in the art.

175. Party Ni admits Adams Fact 175 only to the extent that the '846 application does not identify any particular assay which "ensure[s] that the biological effect observed in an assay is specific to DR5" because such assays would have been evident to one of ordinary skill in the art.

176. Party Ni admits Adams Fact 176.

177. Party Ni admits Adams Fact 177 only to the extent that the assay set forth at page 27, lines 25-33 of the '846 application can be used to identify, *inter alia*, compounds that act as an agonist or antagonist of G-protein coupled cell surface receptor, and that a person of ordinary skill in the art would have know how to adapt the assay for use in identifying agonists or antagonists of DR5.

178. Party Ni admits Adams Fact 178.

179. Party Ni denies Adams Fact 179.

180. Party Ni denies Adams Fact 180.

181. Party Ni admits Adams Fact 181 only to the extent that the exemplary disclosed use of the assay set forth at page 27, lines 25-33 of the '846 application suggests the use of a TNF-family ligand.

182. Party Ni admits Adams Fact 182 only to the extent that the assay set forth at page 27, line 34, through page 28, line 3 of the '846 application refers to measuring a second messenger response, *e.g.*, signal transduction or pH changes, to identify whether a potential compound activates or inhibits DR5.

183. Party Ni is unable to admit or deny Adams Fact 183 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

184. Party Ni denies Adams Fact 184.

185. Party Ni admits Adams Fact 185.

186. Party Ni admits Adams Fact 186 only to the extent that the '846 application does not state that "DR5 ligation can cause calcium flux."

187. Party Ni denies Adams Fact 187.

188. Party Ni admits Adams Fact 188.

189. Party Ni denies Adams Fact 189.

190. Party Ni is unable to admit or deny Adams Fact 190 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

191. Party Ni admits Adams Fact 191.

192. Party Ni admits Adams Fact 192 only to the extent that the assay set forth at page 28, lines 15-25 of the '846 application involves the use of a labeled ligand.

193. Party Ni denies Adams Fact 193.

194. Party Ni admits Adams Fact 194.

195. Party Ni admits Adams Fact 195.

196. Party Ni admits Adams Fact 196.

197. Party Ni admits Adams Fact 197 only to the extent that Tartaglia and Goeddel, *J. Biol. Chem.* *267*:4304-4307 (1992) indicate that anti-TNFR antibodies were added to cells in medium containing 10 μg/ml cycloheximide.

198. Party Ni is unable to admit or deny Adams Fact 198 because the asserted statement (regarding what a person of ordinary skill in the art would have allegedly known by March 17, 1997) is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

199. Party Ni is unable to admit or deny Adams Fact 199 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

200. Party Ni denies Adams Fact 200.

201. Party Ni admits Adams Fact 201 only to the extent that the assay set forth at page 28, line 29, through page 29, line 6 of the '846 application states that "[t]he method involves contacting cells which express the DR5 polypeptide with a candidate compound and a TNF-family ligand . . ."

202. Party Ni admits Adams Fact 202 only to the extent that the assay set forth at page 28, line 29, through page 29, line 6 of the '846 application states that "[t]he method involves contacting cells which express the DR5 polypeptide with a candidate compound and a TNF-family ligand . . ."

203. Party Ni denies Adams Fact 203.

204. Party Ni admits Adams Fact 204 only to the extent that the listed molecules were shown to contain death domains.

205. Party Ni admits Adams Fact 205.

206. Party Ni denies Adams Fact 206.

207. Party Ni admits Adams Fact 207 only to the extent that Feinstein and Kimchi, *TIBS 20*:342-344 (1995) states that "So far there is no evidence implicating the ankyrins, myD88, TUBE, PELLE or N5 in cell-death induction."

208. Party Ni is unable to admit or deny Adams Fact 208 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence; also, the term "varied" is too ambiguous to allow Party Ni to admit or deny this fact.

209. Party Ni admits Adams Fact 209.

210. Party Ni admits Adams Fact 210 only to the extent that Liu *et al.*, *Cell 87*:565-576 (1996) states that "[t]hrough its type 1 receptor (TNFR1), the cytokine TNF elicits an unusually wide range of biological responses, including inflammation, tumor necrosis, cell proliferation, differentiation, and apoptosis."

211. Party Ni denies Adams Fact 211.

212. Party Ni denies Adams Fact 212.

213. Party Ni admits Adams Fact 213 only to the extent that it was known in the art by March 17, 1997 that TNFR-1 could activate NF-κB.

214. Party Ni denies Adams Fact 214.

215. Party Ni admits Adams Fact 215 only to the extent that Mapara and Bargon, *Eur. J. Immunol. 23*:702-708 (1993) refer to a "singular case" in which anti-APO-1 antibody induced proliferation of BCLL cells.

216. Party Ni admits Adams Fact 216 only to the extent that the quoted language is found in Chinnaiyan *et al.*, *Science 274*:990-992 (1996).

217. Party Ni denies Adams Fact 217.

218. Party Ni is unable to admit or deny Adams Fact 218 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

219. Party Ni denies Adams Fact 219.

220. Party Ni admits Adams Fact 220 with the qualification that Rabizadeh *et al.* failed to control for the effects of NGF on Trk receptors, as recognized in later papers such as Carter, *et al.*, *Neuron 18*:187-190 (1997) ("the interpretation of these earlier experiments was however, complicated by the possible presence of full-length Trk receptors, a complication more explicitly avoided in recent experiments.")

221. Party Ni denies Adams Fact 221.

222. Party Ni denies Adams Fact 222.

223. Party Ni is unable to admit or deny Adams Fact 223 because it is unclear what is meant by "little discussion."

224. Party Ni admits Adams Fact 224.

225. Party Ni admits Adams Fact 225.

226. Party Ni admits Adams Fact 226.

227. Party Ni admits Adams Fact 227 only to the extent that Hess and Engelmann, *J. Exp. Med. 183*:159-167 (1996) state that "[a]t the amino acid level these regions show a chemical similarity of 26% for CD40 and p55TNFR, 39% for CD40 and Fas . . ." and that Sato *et al.*, *FEBS Lett. 358*:113-118 (1995) states that "[a] region within the cytoplasmic domain of CD40 however has limited homology to a conserved domain found in the cytosolic tails of p75-NGF-R (22%), TNF-R1 (31%), and Fas (41%)."

228. Party Ni admits Adams Fact 228.

229. Party Ni denies Adams Fact 229.

230. Party Ni admits Adams Fact 230 only to the extent that Nagata, *Cell 88*:355-365 (1997) illustrates the recruitment of intracellular adaptor proteins in Fas and TNFR1 signaling.

231. Party Ni admits Adams Fact 231.

232. Party Ni admits Adams Fact 232.

233. Party Ni is unable to admit or deny Adams Fact 233 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

234. Party Ni denies Adams Fact 234.

235. Party Ni admits Adams Fact 235.

236. Party Ni admits Adams Fact 236.

237. Party Ni admits Adams Fact 237.

238. Party Ni admits Adams Fact 238 only to the extent that the '846 application states that "Since the location of these domains have been predicted by computer graphics, one of ordinary skill would appreciated that the amino acid residues constituting these domains may vary slightly (e.g., by about 1 to 15 residues) depending on the criteria used to define the domain."

239. Party Ni denies Adams Fact 239.

240. Party Ni admits Adams Fact 240 only to the extent that Brojatsch *et al.*, *Cell 87*:845-855 (1996) refers to "residues of TNFR1 that are essential for cell killing."

241. Party Ni denies Adams Fact 241.

242. Party Ni denies Adams Fact 242.

243. Party Ni is unable to admit or deny Adams Fact 243 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not supported by any cited evidence.

244. Party Ni is unable to admit or deny Adams Fact 244 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

245. Party Ni admits Adams Fact 245 only to the extent that this list is not exhaustive.

246. Party Ni is unable to admit or deny Adams Fact 246 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

247. Party Ni denies Adams Fact 247.

248. Party Ni admits Adams Fact 248.

249. Party Ni denies Adams Fact 249.

250. Party Ni denies Adams Fact 250.

251. Party Ni denies Adams Fact 251.

252. Party Ni admits Adams Fact 252.

253. Party Ni admits Adams Fact 253.

254. Party Ni admits Adams Fact 254 only to the extent that the *In re Rezulin* decision stems from a *Daubert* hearing.

255. Party Ni admits Adams Fact 255.

256. Party Ni admits Adams Fact 256 only to the extent that in *In re Rezulin*, the court states of Dr. Reed's testimony, "His testimony therefore is relevant only to the extent that it provides support for the other experts --principally Dr. Smith -- who are willing to draw that conclusion." (*In re Rezulin*, 369. F.Supp.2d at 40).

257. Party Ni admits Adams Fact 257.

258. Party Ni admits Adams Fact 258 only to the extent that the District Court made comments directed to Dr. Reed's testimony in this proceeding.

259. Party Ni admits Adams Fact 259 only to the extent that the District Court made comments directed to Dr. Reed's testimony in this proceeding.

260. Party Ni admits Adams Fact 260 only to the extent that the District Court made comments directed to the plaintiff's experts in this proceeding.

261. Party Ni admits Adams Fact 261 only to the extent that the District Court made comments directed to the plaintiff's experts in this proceeding.

262. Party Ni admits Adams Fact 262.

263. Party Ni denies Adams Fact 263.

264. Party Ni denies Adams Fact 264.

265. Party Ni is unable to admit or deny Adams Fact 265 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

266. Party Ni admits Adams Fact 266 only to the extent as of March 17, 1997, CD40, in some circumstances, was shown to regulate signal transduction pathways leading to apoptosis.

267. Party Ni admits Adams Fact 267.

268. Party Ni admits Adams Fact 268 only to the extent that Dr. Reed does not state in his Declaration that TNFR family members can inhibit apoptosis upon ligand binding.

269. Party Ni admits Adams Fact 269 only to the extent that the papers cited by Adams also state that TNFR-1 also has the function of inducing apoptosis.

270. Party Ni denies Adams Fact 270.

271. Party Ni admits Adams Fact 271.

272. Party Ni is unable to admit or deny Adams Fact 272 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

273. Party Ni denies Adams Fact 273.

274. Party Ni admits Adams Fact 274.

275. Party Ni admits Adams Fact 275 only to the extent that the quoted language is found in the publication entitled "Apoptosis Database."

276. Party Ni admits to Adams Fact 276 only to the extent that the asserted statement is found in Table 2 of the publication entitled "Apoptosis Database."

277. Party Ni admits Adams Fact 277 only to the extent that the quoted language is found in the publication entitled "The Domains of Apoptosis: A Genomics Perspective."

278. Party Ni is unable to admit or deny Adams Fact 278 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

279. Party Ni denies Adams Fact 279.

280. Party Ni denies Adams Fact 280.

281. Party Ni is unable to admit or deny Adams Fact 281 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

282. Party Ni denies Adams Fact 282.

283. Party Ni denies Adams Fact 283.

284. Party Ni admits Adams Fact 284 only to the extent that the experiment described in paragraph 25 of Dr. Reed's Declaration would have been routine for one of ordinary skill in the art.

285. Party Ni is unable to admit or deny Adams Fact 285 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

286. Party Ni is unable to admit or deny Adams Fact 286 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

287. Party Ni admits Adams Fact 287.

288. Party Ni admits Adams Fact 288 only to the extent that Dr. Reed states at paragraph 24 of his Declaration that "It was also known in March 17, 1997 that such aggregation could be caused by (i) ligand binding to the death receptor, (ii) antibody binding to the death receptor, or (iii) merely overexpressing the death receptor to cause aggregation."

289. Party Ni denies Adams Fact 289.

290. Party Ni denies Adams Fact 290.

291. Party Ni admits Adams Fact 291 only to the extent that Dr. Reed does not state in his declaration that TNFα binding to TNFR1 activates the NF-κB pathway.

292. Party Ni denies Adams Fact 292.

293. Party Ni denies Adams Fact 293.

294. Party Ni admits Adams Fact 294.

295. Party Ni denies Adams Fact 295.

296. Party Ni is unable to admit or deny Adams Fact 296 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

297. Party Ni is unable to admit or deny Adams Fact 297 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

298. Party Ni admits Adams Fact 298 only to the extent that Dr. Reed identifies p75 NTR as a TNF receptor.

299. Party Ni admits Adams Fact 299 only to the extent that Dr. Reed does not state the degree of sequence identity or similarity between p75 NGFR and DR3, Fas or TNFR1.

300. Party Ni admits Adams Fact 300 only to the extent that Dr. Reed does not discuss the function of p75 NGFR.

301. Party Ni is unable to admit or deny Adams Fact 301 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

302. Party Ni denies Adams Fact 302.

303. Party Ni admits Adams Fact 303 only to the extent that Dr. Reed states in paragraph 30 of his Declaration, "For example, the CRD of the TRAIL-R2 sequence described by Ni, et al.., shares: 22.4 % homology to Fas/CD95; 30% homology to TNFR1a; and 34.5% homology to DR3, based on an analysis undertaken using Lipman-Pearson Protein Alignment . . ."

304. Party Ni admits Adams Fact 304 only to the extent that Dr. Reed states in paragraph 31 of his Declaration, "For example, the death domain of TRAIL-R2 reported by Ni shares: 21.1 % to Fas/CD95; 32.1% to TNFR1a; and 32.8% to DR3, based on an analysis undertaken using Lipman-Pearson Protein Alignment . . ."

305. Party Ni is unable to admit or deny Adams Fact 305 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

306. Party Ni admits Adams Fact 306.

307. Party Ni denies Adams Fact 307.

308. Party Ni admits Adams Fact 308 only to the extent that Dr. Reed states that the nature of the invention is monoclonal antibodies. (Exhibit 2064, ¶ 35(a))

309. Party Ni denies Adams Fact 309.

310. Party Ni admits Adams Fact 310 only to the extent that Dr. Reed states at paragraph 35(b) of his Declaration that "The state of the art as it existed by March 17, 1997, which included demonstrations by others that agonistic and antagonistic antibodies could be made that bind to the death receptors Fas and TNFR1, proteins highly similar to DR5 . . ."

311. Party Ni is unable to admit or deny Adams Fact 311 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

312. Party Ni is unable to admit or deny Adams Fact 312 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

313. Party Ni is unable to admit or deny Adams Fact 313 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

314. Party Ni is unable to admit or deny Adams Fact 314 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

315. Party Ni is unable to admit or deny Adams Fact 315 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

316. Party Ni admits Adams Fact 316 only to the extent that the '846 application states, "The effects of TNF family ligands and TNF family receptors are varied and influence numerous functions, both normal and abnormal, in the biological processes of the mammalian system." The '846 application also states, "As indicated, such cellular responses include not only normal physiological responses to TNF-family ligands, but also diseases associated with increased apoptosis or the inhibition of apoptosis."

317. Party Ni denies Adams Fact 317.

318. Party Ni is unable to admit or deny Adams Fact 318 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

319. Party Ni denies Adams Fact 319.

320. Party Ni denies Adams Fact 320.

321. Party Ni denies Adams Fact 321.

322. Party Ni admits Adams Fact 322.

323. Party Ni denies Adams Fact 323.

324. Party Ni denies Adams Fact 324.

325. Party Ni admits Adams Fact 325 only to the extent that Dr. Reed states at paragraph 35(f) of his Declaration that "The existence of working examples (*i.e.*, experiments that were actually

carried out) in the March 17, 1997 application, although the March 17, 1997 application does not exemplify experiments that were actually carried out on agonistic and antagonistic antibodies, the absence of such examples would not prevent persons of ordinary skill in the art from obtaining and using such antibodies; . . ."

326. Party Ni denies Adams Fact 326.

327. Party Ni denies Adams Fact 327.

328. Party Ni denies Adams Fact 328.

329. Party Ni denies Adams Fact 329.

330. Party Ni admit Adams Fact 330 only to the extent that Dr. Reed states at paragraph 35(g) of his Declaration that:

> The quantity of experimentation needed, based on the content of the March 17, 1997 application, to make and use agonistic and antagonistic antibodies that bind to DR5; although a person of ordinary skill in the art would need to screen a number of antibodies to identify agonistic and antagonistic monoclonal antibodies that bind to the ECD of DR5, such screening would have been routine for a person of ordinary skill in the art by March 17, 1997.

331. Party Ni denies Adams Fact 331.

332. Party Ni is unable to admit or deny Adams Fact 332 because the asserted statement is not a *fact* but rather an *opinion* of Dr. Karin and is not directly supported by the cited evidence.

333. Party Ni denies Adams Fact 333.

334. Party Ni denies Adams Fact 334.

APPENDIX C: ADDITIONAL MATERIAL FACTS

In accordance with Standing Order ¶ 14.4 (c), Ni asserts that the following additional material facts were not set out in Ni Substantive Motion 3 because these additional facts address issues and/or facts that were raised in the first instance in Adams Opposition 3.

Overview

Summary of Adams' Arguments

335. It is stated in Adams Opposition 3 that "Adams opposes the relief requested in Ni Substantive Motion 3 ('Ni's Motion')." (Adams Opposition 3, page 1, line 2).

336. It is stated in Adams Opposition 3 that:

> Ni's earlier-filed applications do not disclose: 1) a complete or partial structure of an antagonist or agonist antibody according to any one of the Counts; 2) any correlation between the particular structure an antibody must possess and its ability to act as an agonist or antagonist of a Death Receptor 5 ("DR5"); 3) any other distinguishing physical properties or an antagonist or agonist antibody according to any one of the Counts; or 4) a deposit of a cell line that produces an antibody meeting the requirements of any of the Counts.

(Adams Opposition 3, page 2, lines 3-8).

337. It is stated in Adams Opposition 3 that:

> Ni asserts the subject matter of any one of the Counts can be adequately described and enabled by disclosure of a cDNA and a deduced amino acid sequence of a DR5 coupled with a recognition, by way of computer-based sequence alignment, that a DR5 shares some level of sequence homology to other Tumor Necrosis Factor Receptor ("TNFR") proteins. Ni's position is that once such receptor sequence information is obtained, antagonist and agonist antibodies of a DR5 can be achieved through routine antibody production and screening.

(Adams Opposition 3, page 2, lines 14-20).

338. It is stated in Adams Opposition 3 that "[t]here is no legal foundation to support Ni's theory of written description. The case law governing written description clearly requires disclosure of structural or other physical properties of the compound that is the subject of the Counts." (Adams Opposition 3, page 2, line 24, through page 2, line 2).

339. It is stated in Adams Opposition 3 that:

> Ni's arguments also wholly fail to account for the complex and unpredictable nature of the involved technology -- despite the acknowledgement in the disclosure of Ni's own applications that the TNF family of ligands and receptors is one of the most biologically diverse ("pleiotropic") protein families known. Indeed, Ni and Dr. Reed fail to explain that the known death domain-containing TNFR family members, several of which Ni and Dr. Reed allege the DR5 sequences share "significant homology to, themselves exhibit diverse biological effects when bound by their respective cognate ligands.

(Adams Opposition 3, page 2, lines 15-21).

340. It is stated in Adams Opposition 3 that "Ni's March 17, 1997, application does not teach the biological effects exhibited when a DR5 binds a cognate ligand; indeed, it does not even identify a cognate ligand of a DR5." (Adams Opposition 3, page 3, line 23 through page 3, line 1).

341. It is stated in Adams Opposition 3 that "none of Ni's earlier-filed applications describe screening methods that a person of ordinary skill in the art would follow to identify a particular monoclonal or polyclonal compound defined by one of the Counts." (Adams Opposition 3, page 4, lines 1-3).

342. It is stated in Adams Opposition 3 that Ni and Dr. Reed fail to "acknowledge and address the substantive distinctions between a monoclonal and a non-monoclonal antibody compound in

the context of the Counts." (Adams Opposition 3, page 4, lines 18-20). It is also stated in Adams Opposition 3 that "Ni's Motion and Dr. Reed's testimony utterly fail to acknowledge and address the technical distinctions between a monoclonal and non-monoclonal antibody in the context of the Counts." (Adams Opposition 3, page 24, lines 5-7).

Adams Has Provided No Basis for Challenging Dr. Reed's Testimony

343. Adams and Dr. Karin have made several assertions challenging Dr. Reed's testimony and his credibility. (Adams Opposition 3, page 4, lines 8-17; Adams Opposition 3, page 25, lines 5-10; Adams Opposition 3, pages B-30 through B-44 (Adams Facts 252-332); Exhibit 1086, ¶¶ 82, 93, 95-98, 102, 122-124, and 134-141).

Statements Made by A District Court in an Unrelated Legal Proceeding

344. It is stated in Adams Opposition 3 that:

> the Board should carefully scrutinize the testimony of Dr. Reed and should accord it little weight in deciding Ni's Motion. A federal District Court strongly disagreed with the notion that Dr. Reed's credentials and credibility are "beyond challenge." In this interference, as he did before the District Court, Dr. Reed ignored a large amount of scientific information, including his own publications, that call many aspects of his testimony into question. (*See*, Facts 252-261).

(Adams Opposition 3, page 25, lines 5-10).

345. Adams' statement in Opposition 3 regarding a "federal District Court [that] strongly disagreed with the notion that Dr. Reed's credentials and credibility are 'beyond challenge'" refers to *In re Rezulin Products Liability Litigation*, 369 F.Supp. 2d. 398 (S.D.N.Y. 2005) ("the *Rezulin* decision"). (Adams Opposition 3, page B-30 (Adams Fact 253)).

346. The *Rezulin* decision does not relate to patents or interference-related issues. (*Id.*)

347. Adams had the opportunity to cross-examine Dr. Reed to address issues such as the scientific information that he considered in preparation of his declaration and whether or not he "ignored" any information.

348. Adams intentionally chose not to cross-examine Dr. Reed. (Exhibit 2129).

Dr. Reed's Scientific Publications do Not Refute His Testimony

349. It is stated in Adams Opposition 3 that "Dr. Reed's testimony is so oversimplified that in many respects it directly conflicts with statements in his own peer-reviewed publications." (Adams Opposition 3, page 4, lines 8-9).

350. It is stated in Adams Opposition 3 that "Dr. Reed does not explain that publicly available information, including his own publications, expressly refute the notion that the mere presence of a death domain motif in a TNF receptor establishes that an "agonist" of the receptor will induce apoptosis when it binds to the receptor." (Adams Opposition 3, page 4, lines 14-17).

351. In support of the notion that Dr. Reed's own publications refute his testimony regarding the presence of a death domain in TNFRs, Adams has pointed to a passage from Doctor *et al.*, *Cell Death and Differentiation 10*:621-633 (2003). (Adams Opposition 3, page B-34 (Adams Fact 275); Exhibit 1095, page 622, column 2, first paragraph).

352. The passage from Doctor *et al.*, *Cell Death and Differentiation 10*:621-633 (2003) cited at Adams Fact 275 does not relate to death domains in TNFRs. (Exhibit 1095, page 622, column 2, first paragraph).

353. The passage from Doctor *et al.*, *Cell Death and Differentiation 10*:621-633 (2003) cited at Adams Fact 275 does not indicate that death domain-containing TNFRs do not induce apoptosis. Rather, the cited passages simply refers to death domains in *proteins* generally:

> Although the domains may be in several *proteins* involved in apoptosis, the mere presence of the domain does not guarantee an apoptotic function. Nine of the 13 domains are also found in *proteins* that do not have direct involvement in apoptosis, as indicated by their Swiss-Prot annotation. Thus, the presence of a domain cannot be used to automatically define a *protein's* involvement in apoptosis.

(Exhibit 1095, page 622, column 2, first paragraph, emphasis added).

354. In support of the notion that Dr. Reed's own publications refute his testimony regarding the presence of a death domain in TNFRs, Adams has pointed to a passage from Reed *et al.*, *Sci. STKE 2004*, re9 (2004). (Adams Opposition 3, page B-34 (Adams Fact 277); Exhibit 1096, page 10, column 2, first paragraph).

355. The passage from Reed *et al.*, *Sci. STKE 2004*, re9 (2004) cited at Adams Fact 277 does not indicate that death domain-containing TNFRs do not induce apoptosis. Rather, the cited passage indicates that, under certain conditions, TNFR1 and DR3 elicit "robust apoptotic responses." (Exhibit 1096, page 10, column 2, first paragraph).

It Was Entirely Reasonable and Consistent With the Prevailing Views in the Art for Dr. Reed Not to Include p75 NGFR or CD40 in His List of Recognized Death Receptors

356. It is stated in the Declaration of Dr. Reed that "[b]y March 1997, three death receptors were recognized, including TNFR1 (CD120a), Fas (APO1; CD95), and DR3 (TRAMP, WSL-1; Apo-3). Each of these receptors was known by March 17, 1997 to induce cell death by apoptosis." (Exhibit 2064, ¶ 20).

357. Dr. Karin stated that "[a]pplying the rationale used in [Dr. Reed's] Declaration, the 'death receptors' known by March 17, 1997, would include at least TNFR1, Fas, DR3 and p75 NGFR. Nonetheless, Dr. Reed only lists TNFR1, Fas and DR3 as the known death receptors as of March 17, 1997." (Exhibit 1086, ¶ 114).

358. Dr. Karin stated that:

> Thus, despite the fact that the degree of sequence identity or similarity of p75 NGFR to TNFR, Fas and DR3 may be within the same range as DR5 and these three TNFR family members, neither the '846 application nor Dr. Reed discuss p75 NGFR. This may be because NGFR is an example of a TNFR family member with a death domain that does not induce apoptosis upon ligand binding and, thus contradicts Dr. Reed's sweeping conclusions regarding the correlation of sequence identity or similarity and receptor function.

(Exhibit 1086, ¶ 123).

359. Dr. Karin stated that "[u]nder Dr. Reed's rationale as expressed in paragraph 22 of his Declaration, CD40 is a TNFR with a region having "significant" homology to a death domain, and accordingly would be classified, using his rationale, as a "death receptor." (Exhibit 1086, ¶ 124).

360. Chinnaiyan *et al.*, *Science* 274:990-992 (1996) discusses the identification of DR3 and refers to it as "a third cell death receptor" along with CD95 [Fas] and TNFR-1. (Exhibit 2065, page 992, first column, second full paragraph).

361. Chinnaiyan *et al.*, *Science* 274:990-992 (1996) does not include p75 NGFR or CD40 in the list of known death receptors. (Exhibit 2065, page 992, first column, second full paragraph).

362. Dr. Karin acknowledged on cross-examination that the list of death receptors set forth in Chinnaiyan *et al.*, *Science* 274:990-992 (1996) (*i.e.*, CD95, TNFR-1 and DR3) is the same list of death receptors that is provided in Dr. Reed's declaration. (Exhibit 2161, page 62, lines 11-17; Exhibit 2162, disk 1, 11:09:01)

363. Liu *et al.*, *Cell 87*:565-576 (1996), which includes Dr. Karin as an author, states that "TNFR1 and Fas are unique among the TNF receptor family in having cytoplasmic death domains." (Exhibit 1046, sentence bridging pages 570-571).

364. Liu *et al.*, *Cell 87*:565-576 (1996) does not include p75 NGFR or CD40 in the list of molecules that are "unique among the TNF receptor family in having cytoplasmic death domains." (Exhibit 1046, sentence bridging pages 570-571).

365. Liu *et al.*, *Cell 87*:565-576 (1996) states that "CD40 lacks a death domain and is unable to trigger apoptosis." (Exhibit 1046, page 572, bottom right column).

366. On cross-examination, Dr. Karin acknowledged that, although he was aware of Liu *et al.*, *Cell 87*:565-576 (1996) which states that "CD40 lacks a death domain and is unable to trigger apoptosis," Dr. Karin did not cite this paper in paragraph 124 of his declaration which asserts that "[i]t had been reported, prior to March 17, 1997, that CD40 had an intracellular region that shared sequence homology with the death domains of NGFR (22%), TNFR (26-31%) and Fas (39-41%)." (Exhibit 2161, page 65, lines 9-24; Exhibit 1086, paragraph 124; Exhibit 2162, disk 1, 11:14:36).

367. Marsters *et al.*, *Curr. Biol. 6*:1669-1676 (1996), which includes Genentech's Avi Ashkenazi as an author, states that "[t]wo receptors that contain the so-called 'death domain' have been

described to date: tumor necrosis factor receptor 1 (TNFR1) and Fas/Apo-1 (CD95)." (Exhibit 2066, page 1669, Background section).

368. Marsters *et al.*, *Curr. Biol.* *6*:1669-1676 (1996) states that "[t]hese results identify Apo-3 as a third member of the TNFR family that activates apoptosis, and suggest that Apo-3, TNFR1 and CD95 engage a common apoptotic cell-death machinery." (Exhibit 2066, page 1669, Conclusions section).

369. Marsters *et al.*, *Curr. Biol.* *6*:1669-1676 (1996) states that "[t]wo TNFR family members, TNFR1 and Fas/Apo-1 (CD95) can activate apoptotic cell death. These two receptors have additional homology in their intracellular domain (ICD), in an oligomerization interface known as the death domain." (Exhibit 2066, page 1669, left column (internal citations omitted)).

370. Marsters *et al.*, *Curr. Biol.* *6*:1669-1676 (1996) includes amino acid sequence alignments between Apo-3, TNFR1 and CD95. (Exhibit 2066, page 1670, Figure 1(b) and (c)).

371. Marsters *et al.*, *Curr. Biol.* *6*:1669-1676 (1996) does not include p75 NGFR or CD40 in its discussion of TNFR members that can activate cell death and include a death domain. (Exhibit 2066).

372. Marsters *et al.*, *Curr. Biol.* *6*:1669-1676 (1996) does not include p75 NGFR or CD40 in the alignment of death domain sequences. (Exhibit 2066, page 1670, Figure 1(c)).

373. Dr. Karin acknowledged on cross-examination that the list of death receptors mentioned in Marsters *et al.*, *Curr. Biol.* *6*:1669-1676 (1996) (*i.e.*, Apo-3, TNFR1 and CD95) is the same

list of death receptors that is provided in Dr. Reed's declaration. (Exhibit 2161, page 69, lines 10-13; Exhibit 2162, disk 1, 11:20:06).

374. Despite the fact that the scientific papers by Chinnaiyan *et al.* and Marsters *et al.* only list TNFR-1, Fas, and DR-3 (Apo-3) as death domain containing TNFR receptors, and Liu *et al.*(a paper which Dr. Karin co-authored) only list TNFR-1 and Fas as death domain containing TNFR receptors, Dr. Karin stated on cross-examination that he believes as of March 1997 these lists were incomplete. (Exhibit 2161, page 69, lines 16-24; Exhibit 2162, disk 1, 11:20:32).

375. Kitson *et al.*, *Nature 384*:372-375 (1996) refers to the cloning of WSL-1 (DR3), and states that "[w]e have cloned a new member of the TNFR superfamily which, like Fas and TNFR-1, contains a death domain and can trigger rapid apoptosis." (Exhibit 2082, page 374, middle right column; Exhibit 2160, page 374, middle right column).

376. Kitson *et al.*, *Nature 384*:372-375 (1996) does not include p75 NGFR or CD40 in the list of members of the TNFR superfamily which "contain[] a death domain and can trigger rapid apoptosis." (Exhibit 2082, page 374, middle right column; Exhibit 2160, page 374, middle right column).

377. Dr. Karin acknowledged on cross-examination that the list of death domain containing TNFR superfamily members mentioned in Kitson *et al.*, *Nature 384*:372-375 (1996) (*i.e.*, WSL-1, Fas and TNFR-1) is the same list of death receptors that is provided in Dr. Reed's declaration. (Exhibit 2161 page 72, lines 12-16; Exhibit 2162, disk 1, 11:24:19).

378. Nagata, *Cell 88*:555-565 (1997) states that "the cytoplasmic regions [of TNFR receptor family members] have little similarity among the members, except for Fas, TNFR1, DR3/Wsl-1, and [the chicken protein] CAR1." (Exhibit 1065, page 355, bottom right column).

379. Nagata, *Cell 88*:555-565 (1997) states that "[s]o far . . . four death receptors (Fas, TNFR1, DR3/Wsl-1, and CAR1) have been identified." (Exhibit 1065, page 362, second column, first paragraph under *Conclusions and Perspectives*).

380. Nagata, *Cell 88*:555-565 (1997) is a review article published approximately one month before Ni's '846 application was filed. (Exhibit 1065; Exhibit 2062).

381. Nagata, *Cell 88*:555-565 (1997) does not include p75 NGFR or CD40 in the list of death receptors that had been identified by February 1997.

382. Dr. Karin acknowledged on cross-examination that the list of death receptors mentioned in Nagata, *Cell 88*:555-565 (1997), aside from the chicken protein CAR1, is the same list of death receptors that is provided in Dr. Reed's declaration. (Exhibit 2161, page 74, lines 19-25; Exhibit 2162, disk 1, 11:28:13).

383. Ware *et al.*, *The Cytokine Handbook*, Chapter 20, pages 549-550 (1998) identifies Fas, TNFR60, DR3 and CAR1 as death domain-containing TNFRs. (Exhbit 2054, page 550).

384. Ware *et al.*, *The Cytokine Handbook*, Chapter 20, pages 549-550 (1998) does not identify p75 NGFR or CD40 as death domain-containing TNFRs. Exhbit 2054, page 550).

385. Dr. Karin stated that he would have included p75 NGFR as a death domain containing TNFR in December 1996. (Exhibit 2161, page 62, lines 18-20; Exhibit 2162, disk 1, 11:09:18).

386. Vishva Dixit from Genentech sent an email to Dr. Reed, on October 18, 2005, requesting that Dr. Reed provide "a candid appraisal of Avi [Ashkenizi's] academic achievements." (Exhibit 2163).

Dr. Karin's Testimony Should Be Accorded Little Weight By the Board, Except as Admissions Against Adams

Dr. Karin Has Significant Personal Interest in the Outcome of These Proceedings

387. Dr. Karin received a request from Dr. Dixit sometime between August and October, 1995, to write a letter of evaluation of Dr. Avi Ashkenazi. (Exhibit 2161, page 242, line 18, through page 243, line 6; Exhibit 2162, disk 4, 10:53:05).

388. Dr. Karin wrote a letter of recommendation for Dr. Avi Ashkenazi in which Dr. Karin stated that he supported Dr. Ashkenazi's promotion "with great enthusiasm." (Exhibit 2150, last paragraph; Exhibit 2161, page 32, lines 23-24; Exhibit 2162, disk 1, 10:13:06).

389. It is stated in Dr. Karin's letter of recommendation for Dr. Avi Ashkenazi that Dr. Ashkenazi:

> is best known for his work on TRAIL receptors and the entire family of related death receptors. In recent years he has been leading a team focused on turning TRAIL into an effective anti-cancer drug. . . .
>
> His work on TRAIL and other TNF family members is outstanding and pioneering. Avi is an excellent and coherent speaker and is a very well respected scientist in the international cytokine and cancer communities.

(Exhibit 2150, second and third paragraphs).

390. Dr. Karin admitted on cross-examination that he owns 1000 shares of Genentech stock, and that he wished he had 10,000 shares. (Exhibit 2161, page 350, lines 19-21; Exhbit 2162, disk 6, 16:10:56).

391. On March 21, 2006, Genentech's stock (symbol "DNA") was trading at approximately $87/share. (Exhibit 2164).

Adams and Dr. Karin Have Argued that, To Describe Agonistic and Antagonistic Antibodies Against a TNFR, One Must Know Structural Information from a Reference Antibody or Provide a Deposit of a Clone that Produces an Antibody

392. It is stated in Adams Opposition 3 that "[a]s emphasized in the case law, one cannot describe a compound by referring to a function it exhibits without correlating some structure of the compound to the claimed functional characteristics." (Adams Opposition 3, page 10, lines 6-8).

393. It is stated in Adams Opposition 3 that:

> Ni's reliance on the decision in *Noelle* is misplaced and irrelevant in the present proceeding. . . . Simply reciting the identity of a DR5 antigen thus cannot, standing alone, distinguish antibodies meeting the requirements of Count 1 from those of meeting the requirements of Count 2 (and similarly those of Proposed Counts 3 from Count 4).

(Adams Opposition 3, page 20, lines 12-17).

394. It is stated in Adams Opposition 3 that:

> Ni's theory that written description for a specific chemical compound can be established by describing procedures that can be performed by routine experimentation has been soundly rejected in numerous cases [citing *Fiers* and *U. Rochester*] . . . As was the case in *Fiers* and in *University of Rochester*, Ni's research plan should be found insufficient to establish written description for the antibody molecules that are the subject of any one of the Counts.

(Adams Opposition 3, page 17, line 24, through page 19, line 17).

395. It is stated in Adams Opposition 3 that:

> The '846 application does not describe any antibody in terms that a person of ordinary skill in the art would have found useful to identify and describe a particular agonist or antagonist antibody of a DR5. (*See*, Facts 167, 169, and 170). For example, the '846 application does not provide the amino acid sequence of the heavy and light chains of an antibody, or a nucleic acid sequence encoding such heavy and light chains. (*See*, Fact 167). It also does not describe any hybridoma or other type of cell line that produces an antibody that binds to an extracellular domain of a DR5 polypeptide and acts as an agonist or an antagonist of a DR5. (*See*, Fact 168). It further does not disclose any correlation of an antibody structure to the desired functional properties of acting as an agonist or antagonist of a DR5. (*See*, Facts 167-170).

(Adams Opposition 3, page 12, lines 17-25).

396. It is stated in Dr. Karin's Declaration that:

> Once a reference antibody has been produced and identified, a person of ordinary skill in the art would determine the specific amino acid sequences present in the two polypeptide chains of the antibody. Equipped with this information, a particular binding specificity can be associated with a particular amino acid sequence and antibody structure.

(Exhibit 1086, ¶ 55).

397. When asked on cross-examination "how does knowledge of the presence of certain amino acid sequences at the variable region of an antibody, for example, one that induces apoptosis, describe other monoclonal antibodies that induce apoptosis in this subclass?" Dr. Karin responded, "[i]t only tells you about the antibody that you analyzed." (Exhibit 2161, page 289, lines 12 to 24; Exhibit 2162, disk 5, 13:38:30).

398. Dr. Karin affirmed on cross-examination that, in 1997, "if people want to know whether an antibody induces apoptosis they just test it." (Exhibit 2161, page 293, line 25, through page 294, line 4; Exhibit 2162, disk 5, 13:46:16).

It Was Known in the Art That Signaling Through TNFRs Occurs By Receptor Aggregation or Clustering

399. Engelmann *et al., J. Biol. Chem. 265*:14497-14504 (1990) states that "[t]he above observations suggest that aggregation of the TNF receptors, *irrespective of the site on the TNF receptor to which the aggregating agent binds*, is sufficient by itself to trigger a TNF-like effect." (Exhibit 2096, page 14503, middle right column, emphasis added).

400. Tartaglia *et al., Proc. Natl. Acad. Sci. USA 88*:9292-9296 (1991) states that:

> Several reports have described antibodies directed against human TNF-R1 that have agonist properties. These studies demonstrate that *a specific conformational change induced by the TNF molecule itself is probably not responsible for the activation of TNF-R1.* Rather, a nonspecific perturbation, most likely receptor dimerization or aggregation, can be sufficient to signal through this receptor.

(Exhibit 2093, page 9295, middle right column, emphasis added).

401. Boldin *et al., J. Biol. Chem. 270*:387-391 (1995) state that "[s]ignaling by the p55 tumor necrosis factor (TNF) receptor and by the structurally related receptor Fas/APO1 is *initiated by receptor clustering*." (Exhibit 2081, Abstract, emphasis added).

402. Dr. Karin admitted on cross-examination that Engelmann *et al., J. Biol. Chem. 265*:14497-14504 (1990), Tartaglia *et al., Proc. Natl. Acad. Sci. USA 88*:9292-9296 (1991), and Boldin *et al., J. Biol. Chem. 270*:387-391 (1995) indicate that signaling in TNFRs is a consequence

of the receptors coming together (aggregating or clustering). (Exhibit 2161, page 141, lines 16 to 24; page 142, lines 15-18; Exhibit 2162, disk 2, 14:43:25).

403. Fadeel *et al.*, *International Immunol. 9*:201-209 (1997) state that "Fas/APO-11 is a cell surface glycoprotein that mediates programmed cell death or apoptosis *when cross-linked with agonistic anti-Fas or anti-APO-1 mAb or the endogenous Fas/APO-1 ligand*." (Exhibit 2098, Abstract, emphasis added).

404. Fadeel *et al.*, *International Immunol. 9*:201-209 (1997) state that:

> In this report, we examined the *in vitro* biological properties of a panel of anti-human Fas mAb of IgG1 subclass (ZB4, VB3, WB3 and CBE). We found that anti-Fas clone VB3 induced marked apoptotic cell death in Fas/APO-1-expressing Jurkat cells, although this cell killing was delayed when compared to the cytolytic effect medicated by the prototypic anti-Fas antibody of IgM subclass (clone CH-11). The ZB4 antibody, on the other hand, efficiently blocked apoptosis induced by CH-11. The WB3 and CBE clones neither induced or inhibited apoptosis. *These antibodies were all found to recognize one and the same linear site on the Fas/APO-1 molecule, despite their different biological effects*.

(Exhibit 2098, Abstract, emphasis added).

405. Nagata and Golstein, *Science 267*:1449-1456 (1995) states that:

> Signaling by means of Fas leads to apoptotic cell death with characteristic cytoplasmic and nuclear condensation and DNA fragmentation. Triggering this pathway *requires the cross-linking of Fas either with antibodies to Fas, with cells expressing FasL, or with purified FasL*. Similar to TNF, the soluble form of FasL has a trimeric structure in solution. Therefore, it is likely that the *cross-linking of Fas molecules*, rather than just their engagement, leads to further signaling within the cell.

(Exhibit 2140, page 1451, bottom left column, internal citations omitted, emphases added).

406. Chuntharapai *et al.*, *J. Immunol. 166*:4891-4898 (2001) shows that different anti-DR4 antibodies, recognizing different epitopes, nonetheless induced *in vitro* apoptosis to similar extents (Exhibit 2151, page 4895, Table II), and further states that:

> Thus, these results suggest that *recognition of a unique epitope that overlaps with the Apo2L/TRAIL binding site, such as in the case of mAb 4H6, is not essential for anti-tumor activity.* We postulate that the receptor oligomerization by high affinity IgG1 mAbs would be sufficient to mediate the death signal, resulting in tumor growth inhibition.

(Exhibit 2151, page 4895, bottom right column, emphasis added).

Genentech Has Filed Several Patent Applications Claiming Antibodies to Receptors Without Describing Actual Working Examples of Such Antibodies

407. U.S. Patent Appl. No. 10/112,193, filed March 28, 2002, naming Avi J. Ashkenazi as sole inventor and Genentech, Inc. as assignee, includes a claim to agonist monoclonal antibodies which specifically bind to the Apo-3 polypeptide or its extracellular domain sequence. (Exhibit 2152, page 33, claims 12-14).

408. As confirmed by Dr. Karin, U.S. Patent Appl. No. 10/112,193 does not show an actual antibody in the examples. (Exhibit 2161, page 317, lines 16 to 25; Exhibit 2162, disk 6, 14:46:51).

409. U.S. Patent No. 6,689,744, which names Genentech, Inc. as assignee, includes claims that include the use of agonistic anti-Notch polypeptide antibodies. (Exhibit 2153, column 45, line 27, through column 46, line 26 (claims 2-6)).

410. As confirmed by Dr. Karin, U.S. Patent No. 6,689,744, does not show an actual antibody in the examples. (Exhibit 2161, page 320, line 3, through page 321, line 9; Exhibit 2162, disk 6, 14:55:50).

411. U.S. Patent No. 5,910,574, which names Genentech, Inc. as assignee, includes claims directed to agonistic monoclonal antibodies specific for a TRK polypeptide. (Exhibit 2154, column 100, lines 49 to 65 (claims 14 and 15)).

412. As confirmed by Dr. Karin, U.S. Patent No. 5,910,574, does not show an actual antibody in the examples. (Exhibit 2161, page 326, line 11, through page 327, line 8; Exhibit 2162, disk 6, 15:07:32).

Genentech Has Previously Argued that Constructive Reduction to Practice of Agonistic Apo-2 Antibodies Does Not Require an Actual Reduction to Practice

413. Genentech filed U.S. Patent Appl. No. 08/857,216 on May 15, 1997. (Exhibit 2116).

414. The disclosure of U.S. Patent Appl. No. 08/857,216 (Exhibit 2117) is identical to that of Adams' U.S. Patent Appl. No. 60/046,615. (Exhibit 1040).

415. U.S. Appl. No. 09/020,746 was filed on February 9, 1998 as a continuation-in-part of U.S. Patent Appl. No. 08/857,216. (Exhibit 2118, page 2).

416. During prosecution of U.S. Appl. No. 09/020,746, claims directed to agonistic monoclonal antibodies against Apo-2 (*i.e.*, monoclonal antibodies that stimulate apoptosis) were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,072,047. (Exhibit 2120, pages 2-3; Exhibit 2121, pages 1-3 and 5-9).

417. In response to the October 18, 2002 Office Action issued in U.S. Patent Appl. No. 09/029,746, Genentech submitted a Declaration under 37 C.F.R. § 1.131, signed by Dr. Ashkenazi. (Exhibit 2121, pages 8-9; Exhibit 2122).

418. Dr. Avi Ashkenazi asserted in a Rule 131 Declaration dated October 15, 2002 that U.S. Patent Appl. No. 08/857,216, filed on May 15, 1997, "demonstrates both my conception of the claimed invention of the present application and a *constructive reduction to practice* of the invention prior to at least the June 4, 1997 priority filing date of the '047 patent." (Exhibit 2122, paragraph 6, emphasis added).

419. U.S. Patent Appl. No. 08/857,216 does not disclose a working example of an antibody. (Exhibit 2117, page 58, line 18, through page 68, line 14).

420. Party Adams admitted in its Substantive Motion 2 that U.S. Patent Appl. No. 60/046,615 (which is identical to U.S. Patent Appl. No. 08/857,216) "does not describe a particular agonist or antagonist antibody to the Apo-2 receptor." (Adams Substantive Motion 2, page 8, lines 8-9).

421. The disclosure of U.S. Patent Appl. No. 09/020,746 (Exhibit 2119) is identical to that of U.S. Patent Appl. No. 60/074,119. (Exhibit 1039).

422. Dr. Avi Ashkenazi asserted in a Rule 131 Declaration dated December 6, 2002 that U.S. Patent Appl. No. 08/857,216 "demonstrates both my conception of the claimed invention of the present application and a constructive reduction to practice of the invention." (Exhibit 2040, paragraph 6).

423. With regard to U.S. Patent Appl. No. 08/857,216, Dr. Avi Ashkenazi asserted in a Rule 131 Declaration dated December 6, 2002 that:

> In the '216 application, agonist antibodies to the Apo-2 receptor are described. (See, e.g., Page 10, lines 3-5; Page 15, lines 7-10; Page 56, lines 21-23). More particularly, the '216 application discloses that an agonistic Apo-2 antibody may be employed to activate or stimulate apoptosis in mammalian cancer cells (Page 56, lines 21-23). Methods for making Apo-2 antibodies are described on pages 48-56 of the '216 application. Apoptotic activity in mammalian cells is described on, e.g., page 17, lines 1-12, of the '216 application.
>
> The '216 application therefore demonstrates that agonist antibodies which bind Apo-2 receptor and stimulate apoptosis were *conceived and constructively reduced to practice by* the May 15, 1997 filing date of my patent application.

(Exhibit 2040, paragraphs 8 and 9, emphasis added).

424. Dr. Avi Ashkenazi asserted in a Rule 131 Declaration dated January 17, 2003 that U.S. Patent Appl. No. 08/857,216 "demonstrates both my conception of the claimed invention of the present application and a constructive reduction to practice of the invention." (Exhibit 2125, paragraph 4).

425. With regard to U.S. Patent Appl. No. 08/857,216, Dr. Avi Ashkenazi asserted in a Rule 131 Declaration dated January 17, 2003 that:

> In the '216 application, agonist antibodies to the Apo-2 receptor are described. (See, e.g., Page 10, lines 3-5; Page 15, lines 7-10; Page 56, lines 21-23). More particularly, the '216 application discloses that an agonistic Apo-2 antibody may be employed to activate or stimulate apoptosis in mammalian cancer cells (Page 56, lines 21-23). Methods for making Apo-2 antibodies are described on pages 48-56 of the '216 application. Apoptotic activity in mammalian cells is described on, e.g., page 17, lines 1-12, of the '216 application.
>
> The '216 application therefore demonstrates that agonist antibodies which bind Apo-2 receptor and stimulate apoptosis were *conceived*

> *and constructively reduced to practice by* the May 15, 1997 filing date of my patent application.

(Exhibit 2125, paragraphs 6 and 7, emphasis added).

Adams and Dr. Karin Have Advanced A Definition of Agonistic and Antagonistic Antibodies That Is Contradicted By Genentech's and HGS' Specifications As Well As By Several Scientific References

Adam' and Dr. Karin's Definition of Agonists and Antagonists Requires Knowledge of the Biological Effects of Cognate Ligand Binding to the Receptor

426. It is stated in Adams Opposition 3 that "A cognate ligand of a DR5 is not identified in the '846 application, and the effects of binding of a cognate ligand to a DR5 are also not shown in the '846 application. (Adams Opposition 3, page 16, lines 22-23).

427. It is stated in Adams Opposition 3 that:

> One skilled in the art would also appreciate that the functional property of being an agonist or an antagonist of a DR5, as defined by the Counts, is a relative term that is dependent on knowledge of the biological effects that are characteristic of cognate ligand binding to a DR5. Without this knowledge, one could not characterize the biological effects being observed upon antibody binding as being due to "agonistic" or "antagonistic" interactions with the receptor.

(Adams Opposition 3, page 11, lines 1-3).

428. It is stated in Adams Opposition 3 that "the characterization of an antibody as an 'agonist' or 'antagonist' requires information establishing the characteristic biological effects that ensue from binding of a cognate ligand to a DR5." (Adams Opposition 3, page 16, lines 19-21).

429. It is stated in Adams Opposition 3 that "without data correlating the biological effects to those that are characteristic of cognate ligand binding to a DR5, a person of ordinary skill in

the art could not have characterized any composition as being either an "antagonist" or an "agonist" of the receptor." (Adams Opposition 3, page 11, lines 22-24).

430. Dr. Karin stated that:

> The second functional property required by the counts is that the antibody functions as an "agonist" or an "antagonist" of a DR5. This requirement refers to the biological effect(s) or responses exhibited when a cognate ligand binds to a DR5 in a setting where the levels of expression of the receptor are not artificially manipulated.

(Exhibit 1086, ¶ 68).

431. Dr. Karin stated that a representative definition of "agonist" and antagonist" is provided in Goodman and Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition (1996) ("Goodman and Gilman's"), p. 29 bridging p. 30:

> Drugs that bind to physiological receptors and mimic the effects of the endogenous regulatory compounds are termed agonists. Other drugs bind to receptors and do not mimic, but interfere with, the binding of the endogenous agonist. Such compounds, which are themselves devoid of intrinsic regulatory activity, but which produce effects by inhibiting the action of an agonist (e.g., by competition for agonist binding sites), are termed antagonists. [AX-1064, pp. 29 and 30].

(Exhibit 1086, ¶ 69).

432. When asked on cross-examination how he decided to use the definition of "agonists" and "antagonists" set forth in Goodman and Gilman's, Dr. Karin replied: "I'm a professor of pharmacology and this is the textbook of pharmacology, so it was a natural decision." (Exhibit 2161, page 47, lines 14-24; Exhibit 2162, disk 1, 10:45:54).

433. When asked on cross-examination whether he conducted a search of other dictionary definitions other than Goodman and Gilman's to arrive at his definition of "agonists" and

"antagonists," Dr. Karin replied: "No because I teach students about agonist and antagonist and that's the definition that we use, that's a definition that I heard used by other people in my department." (Exhibit 2161, page 108, lines 11-17; Exhibit 2162, disk 2, 13:16:42).

Other Definitions of Agonists and Antagonists Do Not Require Knowledge of the Biological Effects of Cognate Ligand Binding to the Receptor

434. Stedman's Medical Dictionary, 26th edition (1995) defines an agonist as a "drug capable of combining with receptors to initiate drug actions; it possesses affinity and intrinsic activity." (Exhibit 2131, page 38).

435. Dr. Karin admitted on cross-examination that the definition of "agonist" set forth in Stedman's Medical Dictionary, 26th edition (1995) does not say that the cognate ligand identity is required to call something an agonist. (Exhibit 2161, page 109, lines 18 to 21; Exhibit 2162, disk 2, 13:18:42).

436. Dr. Karin admitted on cross-examination that the definition of "agonist" set forth in Stedman's Medical Dictionary, 26th edition (1995) does not say that one needs to know the biological effect that is characteristic of the signal caused by the cognate ligand binding to the receptor, or that one needs to know the consequences of cognate ligand binding. (Exhibit 2161, page 109, line 22, through page 110, line 6; Exhibit 2162, disk 2, 13:18:52).

437. Stedman's Medical Dictionary, 26th edition (1995, page 96) defines an antagonist as "something opposing or resisting the action of another; certain structures, agents, diseases, or physiological processes that tend to neutralize or impede the action or effect of others." (Exhibit 2131, page 96).

438. Dr. Karin admitted on cross-examination that the definition of "antagonist" set forth in Stedman's Medical Dictionary, 26^{th} edition (1995) does not say that one needs to know the cognate ligand to call something an antagonist. (Exhibit 2161, page 110, lines 18 to 22; Exhibit 2162, disk 2, 13:19:05).

439. Dr. Karin admitted on cross-examination that the definition of "antagonist" set forth in Stedman's Medical Dictionary, 26^{th} edition (1995) does not say that one needs to know the biological effects that are characteristic when the cognate ligand binds, or that one needs to know the consequences of cognate ligand binding to the receptor. (Exhibit 2161, page 110, line 23, through page 111, line 7; Exhibit 2162, disk 2, 13:20:18).

440. Lippincott's Illustrated Reviews: Pharmacology, second edition (1997) defines an agonist as "an agent that can bind to a receptor and elicit a response." (Exhibit 2130, page 21, left column; Exhibit 2156, page 21, left column).

441. Dr. Karin admitted on cross-examination that the definition of "agonist" set forth in Lippincott's Illustrated Reviews: Pharmacology, second edition (1997) does not state that one needs to know the consequences of cognate ligand binding to the receptor. (Exhibit 2161, page 112, lines 12 to 15; Exhibit 2162, disk 2, 13:22:51).

442. Dr. Karin admitted on cross-examination that the definition of "agonist" set forth in Lippincott's Illustrated Reviews: Pharmacology, second edition (1997) does not state that one would need to know the biological effects that are characteristic of signaling caused by cognate ligand binding to the receptor. (Exhibit 2161, page 112, lines 16 to 22; Exhibit 2162, disk 2, 13:23:41).

443. Therapeutic Proteins: Pharmacokinetics and Pharmacodynamics (1993) states that "when a drug produces an effect by combining with a receptor, it is termed an agonist. Conversely, a drug that prevents the coupling of such an agonist to a receptor is termed an antagonist." (Exhibit 2132, page 4).

444. Dr. Karin admitted on cross-examination that the definition of "agonist" set forth in Therapeutic Proteins: Pharmacokinetics and Pharmacodynamics (1993) does not require identification of a cognate ligand to characterize a drug as an agonist. (Exhibit 2161, page 114, lines 4 to 7; Exhibit 2162, disk 2, 13:25:33).

445. Dr. Karin admitted on cross-examination that the definition of "agonist" set forth in Therapeutic Proteins: Pharmacokinetics and Pharmacodynamics (1993) does not state that one needs to know the biological effects that are characteristic of signaling caused by cognate ligand binding to the receptor to define something as an agonist, or that one would need to know the consequences of cognate ligand binding to the receptor before one can call something an agonist. (Exhibit 2161, page 114, lines 8 to 17; Exhibit 2162, disk 2, 13:25:48).

446. Dr. Karin admitted on cross-examination that the definition of "antagonist" set forth in Therapeutic Proteins: Pharmacokinetics and Pharmacodynamics (1993) does not say that one needs to know the cognate ligand's identity before calling a drug an antagonist. (Exhibit 2161, page 114, lines 18 to 22; Exhibit 2162, disk 2, 13:26:19).

447. Dr. Karin admitted on cross-examination that the definition of "antagonist" set forth in Therapeutic Proteins: Pharmacokinetics and Pharmacodynamics (1993) does not say that one needs to know the biological effects characteristic of the inhibition of signaling resulting

from cognate ligand binding before one can call something an antagonist. (Exhibit 2161, page 114, line 23 to page 115, line 3; Exhibit 2162, disk 2, 13:26:33).

448. Dr. Karin admitted on cross-examination that the definition of "antagonist" set forth in Therapeutic Proteins: Pharmacokinetics and Pharmacodynamics (1993) does not say that one needs to know the consequences of cognate ligand binding to characterize it as an antagonist. (Exhibit 2161, page 115, lines 4 to 7; Exhibit 2162, disk 2, 13:26:47).

449. Basic Pharmacology (1996) defines an agonist as "a drug that induces an active response by activating receptors." (Exhibit 2133, page 15; Exhibit 2157, page 15).

450. Basic Pharmacology (1996) states that "antagonists form a drug/receptor complex that does not evoke an active response from the cell. Antagonists simply prevent attachment of agonists to the receptor." (Exhibit 2133, page 15; Exhibit 2157, page 15).

451. Dr. Karin admitted on cross-examination that there are multiple dictionary definitions for "agonists" and "antagonists." (Exhibit 2161, page 117, line 18, through page 118, line 5; Exhibit 2162, disk 2, 13:30:14).

Agonistic and Antagonistic Antibodies to Receptors Were Commonly Identified in the Art Without Knowledge of the Ligand

452. Bennett *et al.*, *J. Biol. Chem. 269*:14211-14218 (1994) describe the cloning and characterization of a novel tyrosine kinase receptor, HTK. (Exhibit 2134, Abstract).

453. An agonist for HTK had not been identified at the time Bennett *et al.*, *J. Biol. Chem. 269*:14211-14218 (1994) was published. (Exhibit 2134, page 14217).

454. Bennett *et al.*, *J. Biol. Chem. 269*:14211-14218 (1994), the authors of which are affiliated with Genentech, state that antibodies against the extracellular domain of HTK "were agonistic, inducing Htk tyrosine phosphorylation in transfected NIH3T3 cells," even though, prior to this study, an agonist for HTK had not been identified. (Exhibit 2134, Abstract).

455. Bennett *et al.*, *J. Biol. Chem. 269*:14211-14218 (1994) state that "details of the signaling pathway of Htk may be further explored using antisera as a surrogate ligand." (Exhibit 2134, page 14217, right column).

456. Dr. Karin admitted on cross-examination that Bennett *et al.*, *J. Biol. Chem. 269*:14211-14218 (1994) characterized antibodies that they had made against the HTK receptor as agonistic even though no ligands for HTK had yet been identified. (Exhibit 2161, page 120, lines 18 to 22; Exhibit 2162, disk 2, 13:35:51).

457. Mark *et al.*, *J. Biol. Chem. 269*:10720-10728 (1994), the authors of which are affiliated with Genentech, describe the cloning and characterization of a tyrosine kinase receptor, *rse*. (Exhibit 2135, page 10720, right column).

458. Prior to the publication of Mark *et al.*, *J. Biol. Chem. 269*:10720-10728 (1994), no ligand for *rse* had been identified. (Exhibit 2135, page 10727, right column).

459. Mark *et al.*, *J. Biol. Chem. 269*:10720-10728 (1994) expressed an epitope-tagged version of *rse* (gD-Rse), and used an antibody against the epitope tag as an agonist of the receptor. (Exhibit 2135, page 10720, right column).

460. Mark *et al.*, *J. Biol. Chem. 269*:10720-10728 (1994) state that "[a] general mechanism by which ligands are believed to activate their receptors involves receptor oligomerization. In

some cases, bivalent monoclonal or polyclonal antibodies directed against the ECD of receptor tyrosine kinases can induce the intrinsic tyrosine kinase activity of the receptor." (Exhibit 2135, page 10727, right column).

461. Uckun *et al.*, *J. Biol. Chem. 226*:17478-17485 (1991) refer to the use of the "agonistic anti-CD40 monoclonal antibody G28-5" in examining the biochemical events triggered by the engagement of CD40 (a member of the TNFR family). (Exhibit 2136, Abstract).

462. The ligand for CD40 was identified in Armitage *et al.*, *Nature 357*:80-82 (1992) (Exhibit 2137), which was published approximately 8 months after Uckun *et al.*, *J. Biol. Chem. 226*:17478-17485 (1991) was published. (Exhibit 2136).

463. Dr. Karin admitted on cross-examination that Uckun *et al.*, *J. Biol. Chem. 226*:17478-17485 (1991) called the anti-CD40 monoclonal antibody an "agonist" of CD40 even though the ligand for CD40 had not been discovered. (Exhibit 2161, page 128, lines 3 to 14; Exhibit 2162, disk 2, 13:48:41).

464. Dr. Karin asserted on cross-examination that Uckun *et al.*, *J. Biol. Chem. 226*:17478-17485 (1991) were not accurate in calling the anti-CD40 monoclonal antibody an "agonist" of CD40. (Exhibit 2161, page 128, lines 12-14; Exhibit 2162, disk 2, 13:49:08).

465. Ogasawara *et al.*, *Nature 364*:806-809 (1993) state that "[m]onoclonal antibodies recognizing human Fas antigen, anti-Fas or anti-Apo-1 antibodies, work as agonists and induce apoptosis." (Exhibit 2138, page 807, second column, first paragraph).

466. Dr. Karin admitted on cross-examination that "antibodies that trigger Fas-induced death were identified before the [cognate] ligand was identified." (Exhibit 2161, page 129, lines 13 to 14; page 131, lines 15-16; Exhibit 2162, disk 2, 13:50:50 and disk 2, 13:54:13).

467. On cross-examination, Dr. Karin stated that, even though Ogasawara *et al.*, *Nature 364*:806-809 (1993) called anti-Fas antibodies that induced cell death agonistic antibodies, "it doesn't mean [they] used the word correctly." (Exhibit 2161, page 131, line 23, through page 132, line 2; Exhibit 2162, disk 2, 13:54:39).

468. On cross-examination, Dr. Karin asserted that "[s]cientists are not known for their knowledge of the English language." (Exhibit 2161, page 132, lines 4-5; Exhibit 2162, disk 2, 13:55:01).

469. Suda *et al.*, *Cell 75*:1169-1178 (1993) state that "[s]ome monoclonal antibodies (anti-Fas or anti-APO-1 antibodies) against human or mouse Fas work as agonists and induce apoptosis of the cells inducing Fas, in vitro and in vivo. These results suggested that Fas is a receptor for an unidentified ligand and transduces the apoptotic signal into cells." (Exhibit 2139, page 1169, top right column, internal citations omitted).

470. Dr. Karin admitted on cross-examination that the standard assays for apoptosis are cell condensation, nuclear condensation, formation of hepatropic bodies or DNA laddering. (Exhibit 2161, page 153, lines 5 to 17; Exhibit 2162, disk 3, 15:26:39).

471. When asked on cross-examination "[w]ould you need to know what the cognate ligand is for you to know that apoptosis had occurred," Dr. Karin responded "[n]ot for knowing if it has undergone apoptosis or not."

472. Dr. Karin confirmed on cross-examination that, with assays such as DNA laddering and condensation, one could quickly tell if an antibody induces apoptosis or does not induce apoptosis, and that such screening assays would have been routine. (Exhibit 2161, page 153, line 23, through page 154, line 6; Exhibit 2162, disk 3, 15:27:57).

The Definitions of Agonist and Antagonist Set forth In Ni's and HGS' Disclosures Do Not Require Knowledge of the Cognate Ligand or of the Biological Effect of Cognate Ligand Binding

473. Ni's involved '568 patent defines "agonist" as "naturally occurring and synthetic compounds capable of enhancing or potentiating apoptosis." (Exhibit 2004, column 93, lines 57-58).

474. Ni's involved '568 patent defines "antagonist" as "naturally occurring and synthetic compounds capable of inhibiting apoptosis." (Exhibit 2004, column 93, lines 59-60).

475. Adams' involved '448 application does not explicitly define "agonist" or "antagonist." (Exhibit 1044).

476. Adams' involved '448 application states that "'Biologically active' and 'desired biological activity' for the purposes herein means (1) having the ability to modulate apoptosis (either in an *agonistic or stimulating manner or in an agonistic or blocking manner*) in at least one type of mammalian cell *in vivo* or *ex vivo*; . . ." (Exhibit 1044, page 18, lines 15-19).

Dr. Karin's Definition of Agonists and Antagonists Indicate that Adams Admittedly Does Not Have A Constructive Reduction to Practice of an Agonistic or an Antagonistic Antibody

477. Dr. Karin confirmed on cross-examination that Example 1 of Adams '119 application does not show the biological effects or responses exhibited when a cognate ligand binds to Apo-2

in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 159, lines 6 to 25; Exhibit 2162, disk 3, 15:38:23).

478. Dr. Karin confirmed on cross-examination that Example 2 of Adams '119 application does not show the biological effects or responses exhibited when a cognate ligand binds to Apo-2 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 160, lines 1 to 21; Exhibit 2162, disk 3, 15:41:16).

479. Dr. Karin confirmed on cross-examination that Example 3 of Adams '119 application does not show the biological effects or responses exhibited when a cognate ligand binds to Apo-2 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 160, line 22, through page 161, line 7; Exhibit 2162, disk 3, 15:43:06).

480. Dr. Karin confirmed on cross-examination that Example 4 of Adams '119 application does not show the biological effects or responses exhibited when a cognate ligand binds to Apo-2 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 162, lines 6 to 18; Exhibit 2162, disk 3, 15:46:51).

481. Dr. Karin confirmed on cross-examination that Example 5 of Adams '119 application does not show the biological effects or responses exhibited when a cognate ligand binds to Apo-2 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 161, line 8 to page 162, line 16; Exhibit 2162, disk 3, 15:44:50).

482. Dr. Karin confirmed on cross-examination that the overexpression assay shown in Example 6 of Adams '119 application does not show the biological effects or responses exhibited when a cognate ligand binds to Apo-2 in a setting where the levels of expression of the receptor are

not artificially manipulated. (Exhibit 2161, page 162, line 19 to page 163, line 18; Exhibit 2162, disk 3, 15:49:07).

483. Dr. Karin stated on cross-examination that the assay in Example 6 of Adams '119 application (which does not appear to entail overexpression of Apo-2) is not unambiguous because the signaling shown in this example "could be Apo-2 or it could be another receptor." (Exhibit 2161, page 163, line 24, through page 165, line 14; Exhibit 2162, disk 3, 15:51:09).

484. Dr. Karin confirmed on cross-examination that Examples 7 and 8 of Adams '119 application do not show the biological effects or responses exhibited when a cognate ligand binds to Apo-2 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 165, line 15 to page 166, line 9; Exhibit 2162, disk 3, 15:56:14).

485. Example 9 of Adams '119 application is entitled "Preparation of Monoclonal Antibodies Specific for Apo-2." (Exhibit 1039, page 64, line 13).

486. According to Example 9 of Adams '119 application, Balb/c mice were injected with an Apo-2 ECD immunoadhesin protein. (Exhibit 1039, page 64, lines 14-15).

487. According to Example 9 of Adams '119 application, hybridoma supernatants that tested positive in an ELISA were "further analyzed by FACS analysis using 9D cells." (Exhibit 1039, page 65, lines 31-32).

488. According to Adams 119 application, 9D cells express more than one receptor for Apo-2L, and that "Apo-2L can induce apoptosis in the 9D cells by interacting with either Apo-2 or the DR4 receptor." (Exhibit 1039, page 67, lines 26-28).

489. Dr. Karin stated on cross-examination that Example 9 of Adams '119 application does not include controls and that one cannot tell from Example 9 of Adams '119 application whether the 3F11.39.7 antibody is an Apo-2-specific antibody. (Exhibit 2161, page 166, line 10 to page 167, line 23; Exhibit 2162, disk 3, 15:58:17).

490. Dr. Karin admitted on cross-examination that, because of the absence of controls, Example 9 of Adams '119 application does not unambiguously demonstrate the biological affect of TRAIL on DR5 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 169, lines 10 to 24; Exhibit 2162, disk 3, 16:06:35).

491. Dr. Karin admitted on cross-examination that, because of the absence of controls, Example 10 of Adams '119 application does not unambiguously demonstrate the biological affect of TRAIL on DR5 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 167, line 25 to page 168, line 7; Exhibit 2162, disk 3, 16:03:38).

492. Dr. Karin admitted on cross-examination that Example 11 of Adams '119 application is "difficult to interpret" in view of the fact that the "blocking antibody" used in this Example, 4H6.17.8, induces apoptosis by itself and cross-reacts with DR5. (Exhibit 2161, page 171, line 19, through page 172, line 3; page 175, line 23, through page 176, line 14; Exhibit 2162, disk 3, 16:11:41 and disk 3, 16:19:05; Exhibit 2141, Example 2).

493. Dr. Karin confirmed on cross-examination that Example 12 of Adams '119 application does not show the biological effects of TRAIL on DR5 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 177, lines 3 to 8; Exhibit 2162, disk 3, 16:22:52).

494. Dr. Karin confirmed on cross-examination that Example 13 of Adams '119 application does not show the biological effects of TRAIL on DR5 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 178, lines 17-22; Exhibit 2162, disk 3, 16:25::24).

495. Dr. Karin stated on cross-examination that Adams did not show in any of the 13 Examples presented in the '119 application an effect or response exhibited when a cognate ligand binds to a DR5 in a setting where the levels of expression of the receptor are not artificially manipulated. (Exhibit 2161, page 179, lines 3 to 24; Exhibit 2162, disk 3, 16:26:04).

496. Dr. Karin stated on cross-examination that Adams is not entitled to call the 3F11.39.7 antibody an agonist. (Exhibit 2161, page 179, line 25, through page 180, line 3; Exhibit 2162, disk 3, 16:27:21).

497. Dr. Karin stated on cross-examination that, in view of Goodman and Gilman's definition of "antagonists" as compounds which are devoid of intrinsic regulatory activity, "[i]t's difficult to say" whether Adams' exemplary antibody, 3F11.39.7 would be considered an antagonist. (Exhibit 2161, page 180, line 8, through page 181, line 20; Exhibit 2162, disk 3, 16:27:56).

498. Dr. Karin stated on cross-examination that he (Dr. Karin) could not call the 3F11.39.7 antibody either an agonist or an antagonist. (Exhibit 2161, page 182, lines 4 to 9; Exhibit 2162, disk 3, 16:31:15).

Adams and Dr. Karin Have Failed to Establish That A Person of Ordinary Skill in The Art Would Have Questioned the Asserted Apoptotic Activity of DR5 As Set Forth in the '846 Application

Adams' and Dr. Karin's Arguments Regarding the Pleiotropic Nature of TNFRs are Flawed and Misleading

499. It is stated in Adams Opposition 3 that:

> Further, it is important to understand that the TNFR superfamily is a complex and pleiotropic family of receptor proteins. As of March 1997, a number of proteins had been classified as members of the TNFR superfamily and recognized as having diverse biological functions ranging from induction or suppression of cell proliferation to cell death to inflammation.

(Adams Opposition 3, page 11, lines 9-13).

500. DR5 is not identified in the '846 application as simply a generic member of the TNFR superfamily but as a "death domain containing receptor with the ability to induce apoptosis." (Exhibit 2062, page 6, lines 31-33).

501. The features of a classical TNF family death receptor are (i) signal (leader) peptide; (ii) an extracellular domain, including cysteine-rich domains; (iii) a transmembrane domain; and an intracellular domain, including a death domain. (Exhibit 2064, ¶ 28).

502. Ni's '846 application identifies a signal (or leader) peptide within the full amino acid sequence of DR5. (Exhibit 2062, page 5, lines 3-4; Exhibit 2062, page 6, lines 27-28; Exhibit 2062, Figure 1; Exhibit 2064, ¶ 28).

503. Ni's '846 application identifies an extracellular domain within the full amino acid sequence of DR5, including two cysteine rich domains. (Exhibit 2062, page 5, lines 4-5; Exhibit 2062, page 6, lines 30-31; Exhibit 2062, Figure 1; Exhibit 2064, ¶ 28).

504. Ni's '846 application identifies a transmembrane domain within the full amino acid sequence of DR5. (Exhibit 2062, page 5, lines 5-6; Exhibit 2062, Figure 1; Exhibit 2064, ¶ 28).

505. Ni's '846 application identifies an intracellular domain within the full amino acid sequence of DR5, including a death domain. (Exhibit 2062, page 5, lines 6-7; Exhibit 2062, page 6, lines 31-33; Exhibit 2062, Figure 1; Exhibit 2064, ¶ 28).

506. By March 17, 1997, the known death domain-containing TNFRs that were considered "death receptors" by persons of ordinary skill in the art were Fas, TNFR-1 and DR3. (Exhibit 2064, ¶ 20).

507. By March 17, 1997, it was well-established in the art that Fas induced apoptosis. (Exhibit 2140; page 1451, bottom left column; Exhibit 2066, page 1669, left column; Exhibit 1077, page 321, top left column).

508. By March 17, 1997, it was well-established in the art that TNFR-1 induced apoptosis. (Exhibit 2066, page 1669, left column; Exhibit 1077, page 321, top left column).

509. By March 17, 1997, it was well-established in the art that DR3 induced apoptosis. (Exhibit 2065, page 991, right column; Exhibit 2066, page 1672, left column).

Adams' and Dr. Karin's Arguments Regarding the Correlation Between Death Domains and Apoptosis Induction Are Flawed and Misleading

510. It is stated in Adams Opposition 3 that:

> A person of ordinary skill in the art would have understood that death domain structures or "motifs" are not exclusive to the TNFR family, and that the presence of a death domain structure in a newly identified molecule would not, standing alone, warrant classification of the molecule as a new member of the TNFR family. (*See*, Facts 204 and

> 205). Moreover, by March 17, 1997, a person of ordinary skill in the art would have understood that the mere presence of a death domain structure in a protein does not reveal the function or activity of the molecule, and in particular, does not reveal that the molecule will induce apoptosis upon cognate ligand binding, or even play a role in apoptosis. (*See*, Facts 206 and 235-243). For example, by March 17, 1997, it had been shown that several death domain-containing proteins were not implicated in cell-death induction. (*See*, Fact 207).

(Adams Opposition 3, page 14, lines 14-23).

511. It is stated in Adams Opposition 3 that:

> By March 17, 1997, it had been shown that TNFR1, Fas, DR3, and p75 NGFR each contained intracellular death domain structures. (*See*, Facts 294 and 295). However, it was also known that the mere presence of such death domain structures was not revealing of the functions of those four TNFR family members. (*See*, Facts 204-229)."

(Adams Opposition 3, page 14, line 24, through page 15, line 2).

512. It is stated in Dr. Karin's Declaration that:

> By March 17, 1997, a person of ordinary skill in the art would have known that "death domains" are sequence structure motifs involved in protein-protein interactions and are found in the intracellular regions of a variety of proteins, including FADD (MORT1), TRADD, RIP, Ankryn, the ankryn-related proteins UNC-5 and UNC-44, PELLE, TUBE, DAP-kinase, myD88, N5, p84, pRb, NF-κB2/p100 as well as some but not all members of the TNFR family. (AX-1076, p.343, Fig. 2 and AX-1077, p.322, Fig. 1). Therefore a person of ordinary skill in the art would have understood that death domain structures are not exclusive to the TNFR family, and that the presence of a death domain structure in a newly identified molecule would not, standing alone, warrant classification of the molecule as a new member of the TNFR family.

(Exhibit 1086, ¶ 112).

513. It is stated in Dr. Karin's Declaration that:

> By March 17, 1997, a person of ordinary skill in the art would have understood that the mere presence of a death domain structure in a protein does not reveal the function or activity of the molecule, and in particular, does not reveal that the molecule will induce apoptosis upon ligand binding, or even play a role in apoptosis. For example, by March 17, 1997, it had been shown that several death domain-containing proteins were not implicated in cell-death induction. *See*, AX 1076, p.344, Fig 2 ("so far there is no evidence implicating the ankyrins, myD88, TUBE, PELLE or N5 in cell-death induction.")

(Exhibit 1086, ¶ 113).

514. Dr. Karin admitted on cross-examination that none of the molecules specifically named in paragraph 112 of his declaration (FADD (MORT1), TRADD, RIP, Ankryn, the ankryn-related proteins UNC-5 and UNC-44, PELLE, TUBE, DAP-kinase, myD88, N5, p84, pRb, or NF-κB2/p100) are TNFRs. (Exhibit 2161, page 150, line 21, through page 151, line 6; Exhibit 2162, disk 3, 15:22:02).

515. It is stated in Adams Opposition 3 that:

> By March 17, 1997, a person of ordinary skill in the art would have been familiar with various work, which showed that activation of TNFR1 by TNFα binding under physiological conditions does not result in apoptosis unless additional, artificial measures are taken to inhibit the activation of NF-κB by the same ligand-receptor interaction.

(Adams Opposition 3, page 15, lines 7-10).

516. It is stated in Dr. Karin's Declaration that "the primary function of TNFR1 was known to be the induction of inflammation which is considered as an opposite response to apoptosis." Exhibit 1086, ¶ 115).

517. It is stated in Dr. Karin's Declaration that:

> By March 17, 1997, it was known that Fas receptor could induce proliferation of certain cell types, in addition to an ability to stimulate apoptosis upon binding of a cognate ligand, FasL. (AX-1060, pp. 705-706 and AX-1078, p.2233, Fig. 1). It was also known that Fas ligand activation of the Fas receptor recruited the intracellular adaptor molecule FADD and that FADD was not typically capable of initiating the activation of the NF-κB pathway. *See*, NX-2065, p. 990, col. 1, ¶ 1 ("Activation of CD95 [Fas] recruits the . . . molecule FADD. Although the central role of CD95 is to trigger apoptosis, TNFR-1 can signal an array of diverse biological activities, many of which stem from its ability to activate nuclear factor κB (NF-κB).")

(Exhibit 1086, ¶ 118).

518. Dr. Karin stated on cross-examination that the prevailing opinion in March of 1997 was that the central role of Fas was to trigger apoptosis. (Exhibit 2161, page 247, line 19, through page 248, line 4; Exhibit 2162, disk 4, 11:01:49).

519. Marsters *et al.*, *Curr. Biol. 6*:1669-1676 (1996) state that "[t]he death domain of TNFR1 mediates the activation of programmed cell death (apoptosis) and of the transcription factor NF-κB, whereas the death domain of CD95 only appears to activate apoptosis." (Exhibit 2066, Abstract).

520. On cross-examination, Dr. Karin admitted that Liu *et al.*, *Cell 87*:565-576 (1996), on which Dr. Karin is named an author, shows TNF-α-induced apoptosis in MCF7 cells without inhibiting NF-κB. (Exhibit 2161, page 264, line 22, through page 265, line 20; Exhibit 2162, disk 5, 11:44:19).

521. On cross-examination, Dr. Karin stated that there is a "special situation" with MCF7 because "in these cells it's sufficient to incubate them the TNF and they will undergo apoptosis. You don't really need to add actinomycin-D or cycloheximide." (Exhibit 2161, page 266, lines 8-23; Exhibit 2162, disk 5, 11:46:49).

522. Dr. Karin admitted on cross-examination that Marsters *et al.*, *Curr. Biol. 6*:1669-1676 (1996) state in the *Background* section that the death domain of CD95 only appears to activate apoptosis.

523. Dr. Karin admitted on cross-examination that Herdegen *et al.*, *J. Neurosci*:*18*:5124-5135 (1998) (Exhibit 2147), on which Dr. Karin is listed as the last author, refers to Fas as a "potent mediator of apoptotic cell death." (Exhibit 2161, page 251, lines 7 to 11; Exhibit 2162, disk 4, 11:08:50).

524. Dr. Karin indicated on cross-examination that he would not be surprised to learn that other activities of Fas besides apoptosis induction, are not mentioned in Herdegen *et al.*, *J. Neurosci*:*18*:5124-5135 (1998) (Exhibit 2147). (Exhibit 2161, page 251, line 13, through page 253, line 10; Exhibit 2162, disk 4, 11:09:26).

525. Mapara *et al.*, *Eur. J. Immunol. 23*:702-708 (1993), which is cited at ¶ 118 of Dr. Karin's Declaration to support the assertion that "Fas receptor could induce proliferation of certain cell types," indicates that cells from only one out of ten patients exhibited cell proliferation when treated with anti-Apo-1, and that the authors were surprised by this singular result. (Exhibit 1060, page 706, top left column; Exhibit 2159, page 706, top left column).

526. Dr. Karin admitted on cross-examination that Alderson *et al.*, *J. Exp. Med. 178*:2231-2235 (1993) were able to show induction of proliferation by anti-Fas antibodies only in the presence of an antibody to CD3. (Exhibit 2161, page 260, lines 12 to 15; Exhibit 2162, disk 4, 11:27:43).

527. Despite the results demonstrated in Alderson *et al.*, Dr. Karin stated on cross-examination that showing induction of proliferation by anti-Fas antibodies was not determinative that Fas is capable of inducing proliferation by his standards. (Exhibit 2161, page 263, lines 11-14; Exhibit 2162, disk 5, 11:40:35).

Adams and Dr. Karin Have Failed to Establish That The '846 Application Would Not Have Enabled A Person of Ordinary Skill in The Art to Identify Agonistic and Antagonistic Antibodies to DR5

Adams and Dr. Karin Have Asserted that the Overexpression Assay in the '846 Application Could Not Have Been Used to Identify Agonistic and Antagonistic Antibodies of the Counts

528. It is stated in Adams Opposition 3 that:

> Adams disagrees with Ni's suggestion that Example 5 provides a description of an overexpression assay that a person of ordinary skill in the art could use, standing alone, to determine if a given monoclonal antibody was acting as an agonist or an antagonist of a DR5. As Dr. Karin indicates, simply adding the antibody to cultures containing DR5-transfected cells and observing the biological effect(s) the antibody exerts on those cells would not inform a person of ordinary skill in the art whether the observed results were due to agonistic, antagonistic or other interactions between the antibody and the DR5. (*See*, Fact 160). As previously explained, the lack of any information in the '846 application correlating apoptosis or nay other cellular response to a cognate ligand binding to a DR5 would have precluded a person of ordinary skill in the art from doing so. (*See*, Fact 161).

(Adams Opposition 3, page 15, line 22, through page 16, line 6).

529. Dr. Karin stated in his Declaration that:

> I observe that Dr. Reed has suggested, at paragraph 25 of his Declaration, that conducting an overexpression assay in the absence of cognate ligand to the receptor is the preferred method to demonstrate apoptosis-inducing activity of "DD-containing TNFR-family members." He also observes that performing this type of experiment would have been a matter of routine experimentation for a person of ordinary skill in he art on March 17, 1997. . . . For the reasons

> discussed above, however, I do not agree with Dr. Reed that such an assay, standing alone, would have been the preferred method for demonstrating the apoptosis inducing activity of a new, previously uncharacterized death domain containing TNFR.

(Exhibit 1086, ¶ 95).

Overexpression Assays Were Commonly Performed Prior to 1997 to Determine Whether a TNFR Induced Apoptosis

530. Dr. Karin admitted on cross-examination that overexpressing a death domain-containing TNFR family member would be a method of determining if the receptor, when overexpressed, would signal apoptosis. (Exhibit 2161, page 214, lines 11 to 17; Exhibit 2162, disk 4, 9:20:47).

531. Dr. Karin admitted on cross-examination that overexpressing a death domain-containing TNFR family member to determine if it induced apoptosis was a widely used method before March 1997. (Exhibit 2161, page 214, lines 18 to 21; Exhibit 2162, disk 4, 9:21:29).

532. Dr. Karin acknowledged on cross-examination that Chinnaiyan *et al.*, *Science 274*:990-992 (1996) (Exhibit 2065) states that overexpression of CD95 and TNFR-1 induces apoptosis and therefore, Chinnaiyan *et al.*, used overexpression to study the apoptotic role of DR3. (Exhibit 2161, page 215, line 9, through page 216, line 5; Exhibit 2162, disk 4, 9:23:03).

533. Dr. Karin acknowledged on cross-examination that Kitson *et al.*, *Nature 384*:372-375 (1996) (Exhibit 2082; Exhibit 2160) used overexpression to test for the apoptotic activity of a putative TNFR. (Exhibit 2161, page 222, lines 3 to 8; Exhibit 2162, disk 4, 9:42:53).

534. Dr. Karin acknowledged on cross-examination that Marsters *et al.*, *Curr. Biol. 6*:1669-1676 (1996) (Exhibit 2066) used overexpression to measure whether a new death domain

containing TNFR exhibited apoptotic activity. (Exhibit 2161, page 224, lines 3 to 7; Exhibit 2162, disk 4, 9:48:36).

535. Dr. Karin acknowledged on cross-examination that Bodmer *et al.*, *Immunity 6*:79-88 (1997) (Exhibit 2067) used an overexpression assay to determine if a new death domain-containing TNFR exhibited apoptosis. (Exhibit 2161, page 225, line 22, through page 26, line 4; Exhibit 2162, disk 4, 9:53:33).

536. Dr. Karin acknowledged on cross-examination that Pan *et al.*, *Science 276*:111-113 (1997) (Exhibit 2023) used an overexpression assay to measure whether DR4 exhibited apoptotic activity. (Exhibit 2161, page 229, lines 2 to 7; Exhibit 2162, disk 4, 9:59:51).

537. Dr. Karin acknowledged on cross-examination that Pan *et al.*, *Science 277*:815-818 (1997) (Exhibit 2022) used overexpression to measure whether DR5 exhibited apoptotic activity. (Exhibit 2161, page 230, lines 18-25; Exhibit 2162, disk 4, 10:03:58).

538. Dr. Karin acknowledged on cross-examination that Sheridan *et al.*, *Science 277*:818-821 (1997) (Exhibit 2021) used an overexpression assay to measure whether DR5 exhibited apoptotic activity. (Exhibit 2161, page 232, lines 13 to 18; Exhibit 2162, disk 4, 10:06:50).

539. Dr. Karin acknowledged on cross-examination that Walczak *et al.*, *EMBO J. 16*:5386-5397 (1997) (Exhibit 2144) used an overexpression assay to measure whether TRAIL-R2 exhibited apoptotic activity. (Exhibit 2161, page 234, lines 17 to 23; Exhibit 2162, disk 4, 10:12:49).

540. Dr. Karin acknowledged on cross-examination that MacFarlane *et al.*, *J. Biol. Chem. 272*:25417-25420 (1997) (Exhibit 2145) used an overexpression assay to measure whether

DR5 exhibited apoptotic activity. (Exhibit 2161, page 236, lines 21 to 25; Exhibit 2162, disk 4, 10:17:43).

541. Dr. Karin acknowledged on cross-examination that Wu *et al.*, *Nature Genetics 17:141*-143 (1997) (Exhibit 2146) used an overexpression assay to measure whether DR5 exhibited apoptotic activity. (Exhibit 2161, page 237, lines 19 to 22; Exhibit 2162, disk 4, 10:20:38).

Dr. Karin Failed to Cite in His Declaration Several Papers From 1996-1997 That Directly Contradict His Testimony

542. Dr. Karin stated in his Declaration that "[b]y March 17, 1997, the death domain-containing TNFR family member, p75 NGFR, had been shown to inhibit apoptosis upon binding by its cognate ligand, NGF," and cites Rabizadeh *et al.* (Exhibit 1067) and Chapman *et al.* (Exhibit 1069) to support this assertion. (Exhibit 1086, ¶ 120).

543. On cross-examination, Dr. Karin admitted that Casaccia-Bonnefil *et al.*, *Nature 383*:716-719 (1996) (Exhibit 2127), Frade *et al.*, *Nature 383*:166-168 (1996) (Exhibit 2128), and Carter *et al.*, *Neuron 18*:187-190 (1997) (Exhibit 2129) indicate that, under some conditions, p75 NGFR may induce apoptosis. (Exhibit 2161, page 87, lines 12-16; Exhibit 2162, disk 2, 11:59:39).

544. On cross-examination, Dr. Karin admitted that he did not cite Casaccia-Bonnefil *et al.*, *Nature 383*:716-719 (1996) (Exhibit 2127), Frade *et al.*, *Nature 383*:166-168 (1996) (Exhibit 2128), or Carter *et al.*, *Neuron 18*:187-190 (1997) (Exhibit 2129) in his Declaration. (Exhibit 2161, page 88, lines 7-9; Exhibit 2162, disk 2, 12:00:53).

545. On cross-examination, Dr. Karin agreed that, with respect to the role of p75 NGFR in apoptosis, "the interpretation of the earlier studies of Rabizadeh and Chapman was

complicated by the failure to control for the presence of multiple NGF receptors," but that he did not indicate in ¶ 120 of his Declaration that "it's complicated." (Exhibit 2161, page 87, line 25, through page 88, line 24; Exhibit 2162, disk 2, 12:00:00).

Dr. Karin Was Evasive on Cross-Examination

546. On cross-examination, Dr. Karin stated that, prior to his deposition, he spent two days with Adam's attorneys discussing "the technicalities of being deposed." (Exhibit 2161, page 21, lines 11-20; Exhibit 2162, disk 1, 9:54:37).

547. When asked on cross-examination what "technicalities" Dr. Karin discussed with Adams' attorneys in preparation for his deposition, Dr. Karin replied, "[t]he nature of the questions one may get and how to answer it." (Exhibit 2161, page 21, lines 21-23; Exhibit 2162, disk 1, 9:55:04).

548. On cross-examination, Dr. Karin asserted that, in preparation for his deposition, he did not discuss apoptosis with Adams' attorneys. (Exhibit 2161, page 20, lines 6-7; Exhibit 2162, disk 1, 9:53:07

549. Dr. Karin stated on cross-examination that, during the two days in which he and Adams' attorneys were preparing for the deposition, the word "apoptosis" was mentioned, but not in a scientific context, and "there was no scientific discussion." (Exhibit 2161, page 20, lines 8-16; Exhibit 2162, disk 1, 9:53:13).

550. Dr. Karin stated on cross-examination that, during the two days in which he and Adams' attorneys were preparing for the deposition, the word "TNFR" was mentioned, but only in the

context of "the type of questions I may get." (Exhibit 2161, page 20, line 21, through page 21, line 1; Exhibit 2162, disk 1, 9:53:56).

551. Dr. Karin stated on cross-examination that, if he was asked a question about TNFR, he does not consider that to be a scientific question. (Exhibit 2161, page 21, lines 3-6; Exhibit 2162, disk 1, 9:54:14).

552. Dr. Karin stated on cross-examination that discussions about TNFRs are not in the nature of scientific questions if the questions are asked by a lawyer. (Exhibit 2161, page 22, lines 5-10; Exhibit 2162, disk 1, 9:55:48).

EXHIBIT E

Paper 99
JS
9-15-6

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Richard E. Schafer)

Human Genome Sciences, Inc.
Junior Party
(Patent 6,872,568;
Inventors: Jian Ni, Reiner L. Gentz, Guo-Liang Yu, Craig A. Rosen),

v.

Genentech, Inc.
Senior Party
(Application 10/423,448;
Inventors: Camellia W. Adams, Avi J. Ashkenazi, Anan Chuntharapai, Kyung Jin Kim).

Patent Interference No. 105,361 (RES)

JOINT SUBMISSION OF REVISED TRANSCRIPT
(Of July 27, 2006 Oral Argument)

Pursuant to the Administrative Patent Judges' request, and as discussed in Adams Submission of Non-Revised Transcript (of July 27, 2006 Oral Argument), filed August 25, 2006, the parties hereby jointly submit a revised version of the transcript.

The undersigned is authorized to file this paper on behalf of both parties.

Respectfully submitted,

Jorge A. Goldstein
Attorney for Party Ni
Registration No. 29,021

Date: September 14, 2006
Sterne, Kessler, Goldstein & Fox P.L.L.C.
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583360_1.DOC

CERTIFICATE OF SERVICE

I, Jorge A. Goldstein, hereby certify that a copy of the foregoing JOINT SUBMISSION OF REVISED TRANSCRIPT (Of July 27, 2006 Oral Argument), has been served on the attorney of record for each of Party Adams and Party Rauch via Federal Express on this 14th day of September 2006, addressed as follows:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

(Administrative Patent Judge Richard E. Schafer)

Human Genome Sciences, Inc.

Junior Party

(Patent 6,872,568;

Inventors: Jian Ni, Reiner L. Gentz, Guo-Liang Yu,

Craig Rosen),

v.

Genentech, Inc.

Senior Party

(Application 10/423,448;

Inventors: Camellia W. Adams, Avi J. Ashkenazi,

Anan Chuntharapai, Kyung Jin Kim).

Patent Interference No. 105,361 (RES)

Ni EXHIBIT 2168
Ni v. Adams
Interference No. 105,361

Thursday, July 27, 2006

Alexandria, Virginia

The HEARING in the above-entitled matter came on at 2:00 p.m. pursuant to Notice, at before:

Judge Carolyn Spiegel

Judge Richard ~~Shafer~~ Schafer

Judge Adrian Hanlon

Job No. 175645

Pages 1 - 70

Reported by: Sandy Medford Nelson

Thursday, July 27, 2006

3:00 p.m.

Patent Interference Hearing Human Genome Sciences, Inc. and Genentech, Inc. was held at:

Board of Patent Appeals
Madison Building E
600 Dulaney Street
Alexandria, Virginia 22313
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Pursuant to agreement, before Sandy Medford Nelson, Notary Public of the State of Virginia.

A P P E A R A N C E S

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JUDGE RICHARD ~~SHAFER~~ SCHAFER
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Wendy Lee
Michele ~~Michelle~~ ~~Raile~~ Wales
Joe ~~Schuler~~ Scholler
Sharla ~~Charla~~ Young
Derek ~~Derrick~~ Scott

P R O C E E D I N G S

JUDGE SPIEGEL: We are here today to discuss the pending and currently undecided motions in interference number 105361 between Party Ni, who is assigned to Human Genome Sciences, Incorporated, and Senior Party Adams who's assigned to Genentech, Incorporated. The sitting panel is Judge Adrian Hanlon, myself, Judge Carolyn Spiegel, and Judge Richard Schafer.

What we'd like to do is begin by the counsel introducing themselves, and then we will have Junior Party begin their case presentation. Each side will have 30 minutes. And, if you want to reserve any time for rebuttal, just tell me when you come up.

And, with that, why don't we get started? Senior Party first --

MR. ~~KUSHAN~~ ASHE: Thank you.

JUDGE SPIEGEL: -- for the introduction just because you got up first.

MR. ASHE: My name is Oliver Ashe, and I represent Senior Party Adams. With me today is

backup lead counsel Jeffrey Kushan and Diane Marshang --

JUDGE SPIEGEL: I'm sorry. I can't hear you.

MR. ASHE: Diane Marshang from Genentech and Ed Kenehan from Greenblum & Bernstein, ~~Hon~~ Hanh Nguyen and Wendy Lee. Thank you.

JUDGE SPIEGEL: You're welcome.

MR. GOLDSTEIN: My name is Jorge Goldstein, and I'm together with my co-counsel Eldora Ellison. We represent HGS, and today we have ~~Michelle Raile~~ Michele Wales, Joe ~~Schuler~~ Scholler, ~~Charla~~ Sharla Young and ~~Derrick~~ Derek Scott of Human Genome Sciences.

JUDGE SPIEGEL: Thank you.

MR. GOLDSTEIN: You're welcome.

JUDGE SPIEGEL: Mr. Goldstein, if you could indulge us by starting with your motion number four to substitute count and motion three for benefit, we'd appreciate it.

MR. GOLDSTEIN: Sure, Your Honor.

JUDGE SPIEGEL: Thank you.

MR. GOLDSTEIN: We have requested that

the count, which is presently limited to monoclonal antibodies --

JUDGE SPIEGEL: Can I interrupt you here for --

MR. GOLDSTEIN: Yes.

JUDGE SPIEGEL: -- just a second here? I see you have demonstratives. Do you have copies for the board? Because I, for one, can't see that. I'm sorry. You know, I'm not tall enough.

MR. GOLDSTEIN: That's all right. I have an original.

JUDGE SPIEGEL: Thank you.

MR. GOLDSTEIN: You're welcome.

JUDGE SPIEGEL: And, Mr. Ashe, you've been served copies of this?

MR. ASHE: I believe so, yes. I received it Friday.

MR. GOLDSTEIN: We have served it a few days ago, so I believe that you have our copies.

MR. ASHE: Yes. Thank you.

JUDGE SPIEGEL: Thank you.

MR. GOLDSTEIN: The demo Exhibits 1 and 2

are reproductions of what you have in demo Exhibit 1 and 2, and these are family trees for HGS and Genentech. I would like to reserve five minutes for rebuttal.

JUDGE SPIEGEL: Certainly.

MR. GOLDSTEIN: You requested that I address the motion to substitute the count first.

JUDGE SPIEGEL: If you please.

MR. GOLDSTEIN: Yes. The counts -- there are two counts, one to antagonist monoclonal antibodies and one to agonist monoclonal antibodies, against the Trail R2 receptor, which is an apoptosis-inducing receptor. We have moved to broaden both counts, at least one of the two alternatives, so that the limitation monoclonal antibodies gets dropped in favor of antibodies because our earliest proofs under the Louis v Okada ~~Louie v Kato~~ test do not encompass monoclonal antibodies. They talk about antibodies broadly.

And so, we believe that the justification for broadening the count is based on reasonable grounds. We're not just requesting that the count

be broadened for any old reason and --

JUDGE SPIEGEL: So, if I understand you, the count is directed to the monoclonal antibody to -- and could we use the term DR5, if no one ~~none~~ objects?

MR. GOLDSTEIN: We don't object.

JUDGE SPIEGEL: DR5, which monoclonal antibody is either an agonist or an antagonist thereof, depending on which count?

MR. GOLDSTEIN: Yes.

JUDGE SPIEGEL: So, you're requesting that the count be broadened to just a generic antibody?

MR. GOLDSTEIN: Correct, Your Honor.

JUDGE SPIEGEL: Because your proofs to an antibody which specifically binds to DR5 --

MR. GOLDSTEIN: DR5, that's right. Our best proofs do not recite monoclonal in them, Your Honor. And so --

JUDGE SPIEGEL: But they do recite binding to DR5?

MR. GOLDSTEIN: Well, a combination of

the proofs do, and they will be supplemented at priority phase, but the best proofs that we have -- documentary proofs in hand -- do not recite monoclonal, but they -- but a combination proofs, documentary proofs, recite together antibodies to DR5, yes, Your Honor.

JUDGE SPIEGEL: But you don't have proofs directed solely to an antibody to DR5? You have a series of proofs that somehow gets me there?

MR. GOLDSTEIN: Well, we can make a case -- make a case on priority that shows that we conceived of generating antibodies, not monoclonal -- antibodies to death receptors, and then we have a proof that shows --

JUDGE SPIEGEL: To death receptors generically?

MR. GOLDSTEIN: To any death receptor that is going to be discovered in the future, the earliest proof that we have, at least in hand right now, says that when such a death receptor is discovered and isolated that it would be routine to generate antibodies against it so that one can

make agonist and antagonist antibodies.

A little later in time, there is a proof that shows that such a death receptor, DR5, was actually discovered and isolated and sequenced and identified for function. And those two together show that we have at least documentary proofs that indicate that in the minds of the inventors as corroborated by these proofs in -- had conceived of generating antibodies to DR5.

JUDGE SCHAFER: Mr. Goldstein, let me ask you a question. When you talk about DR5, the counts talks -- and, again, even your proposed change count talks about a specific sequence.

MR. GOLDSTEIN: Yes.

JUDGE SCHAFER: -- DR5 would meet that sequence?

MR. GOLDSTEIN: Yes.

JUDGE SCHAFER: Okay.

MR. GOLDSTEIN: So, our motion under Louis v Okada ~~Louie v Kato,~~ motion four I believe, requests that the count be broadened so that these earliest documentary proofs, which are our best proofs,

meet the broader count.

JUDGE SPIEGEL: So, if I'm hearing you correctly, you have a documentary proof to generating an antibody to any old death receptor past, present, future? And then you have a documentary proof that you have discovered a specific death receptor, DR5?

MR. GOLDSTEIN: Um-hum.

JUDGE SPIEGEL: And, from that, we are supposed to deduce that you have priority proofs of an antibody to DR5 --

MR. GOLDSTEIN: Not from that alone, Your Honor. Not from that alone. Obviously, a priority case will entail testimony from the inventors and corroborating witnesses. This is just corroborating documentary proof. It is not the primary proof.

JUDGE SPIEGEL: No. I'm just inquiring into what your proffered proof actually is.

MR. GOLDSTEIN: Yes. My proffered proof is corroborating proof -- it corroborates the basic, primary proof that we will put forth in our

priority case.

JUDGE SCHAFER: So, your proffer is we can prove to you -- given the opportunity, we can prove to you the conception of an antibody?

MR. GOLDSTEIN: To DR5.

JUDGE SCHAFER: To DR5.

MR. GOLDSTEIN: And we will corroborate that proof --

JUDGE SCHAFER: And, right now, you can't because you would have to -- you would have to prove a monoclonal antibody to be able --

MR. GOLDSTEIN: Well, I can't corroborate it with documentary proof, which is what I want to be able to do. I certainly can have primary evidence by the inventor and corroborating witnesses that they conceived of an antibody that was either an agonist or an antagonist to DR5. But what I want to be able to do is produce corroborating documentary proof because the testimony alone isn't going to be enough.

JUDGE SPIEGEL: To draw to an antibody?

MR. GOLDSTEIN: Exactly.

JUDGE SPIEGEL: Because -- what you're saying is your ~~collaboration~~ corroboration goes to antibodies where generally --

MR. GOLDSTEIN: Exactly, Your Honor. That's right. You then requested that I address the motion for benefit.

JUDGE SPIEGEL: Yes.

MR. GOLDSTEIN: Is that correct?

JUDGE SPIEGEL: Yes, sir.

MR. GOLDSTEIN: Yeah. Well, I have shown in these two -- demo one and demo two -- the HGS family tree on the left in demo one, and the Genentech family tree on the right. Green are the assigned priority dates, and these two green boxes are the involved patent and application of the parties respectively. Yellow are the requested benefit, priority benefit. And in a red/purple I have also indicated the existence of a parallel prosecution that occurred --

JUDGE SPIEGEL: Let's just stop right there. Your motion to benefit goes to benefit for ~~you're~~ your involved --

MR. GOLDSTEIN: Yes.
JUDGE SPIEGEL: -- case.
MR. GOLDSTEIN: Excuse me.
JUDGE SPIEGEL: So, why don't we just stick with the first demonstrative?
MR. GOLDSTEIN: Yes, Your Honor. So, we've asked for benefit all the way back to March 17, 1997. The '846 application, that is the earliest ~~file~~ filed application of either party. This application enables, describes and provides a fully credible utility for the two antibodies -- two embodiments under -- one -- one embodiment under each count for an agonist antibody and for an antagonist antibody.
And, at this point, they are monoclonals and we do enable, describe and provide full utility on how to use ~~to~~ monoclonal agonist antibodies to DR5 and monoclonal antagonistic antibodies for DR5 for these two counts.
The discovery of this molecule by Dr. Ni resulted in a determination that the structure of the molecule, the motifs present in the molecule

and their linear sequence -- the order in which these motifs appear, namely a leader sequence, an extracellular domain with two cysteine-rich domains, a ~~transmembering~~ transmembrane domain, and intracellular domain with a death domain in it, and a homology of portions of these domains compared to prior art death receptors like Fas and DR3 and TNFR1 accurately identified this new molecule as another death receptor.

And this is not any old TNFR as our opponents would like you to believe and argue. This is not any old TNFR. This is a TNFR with ~~the~~ a death domain. And it isn't any old protein with a death domain such as intracellular proteins that are involved in signalling. This is a protein with a death domain. It's also a TNFR.

So, the combination of both subsets, the TNFR structure, the homology to prior art and the presence of a death domain in the TNFR accurately identified the molecule as a death receptor. And, in fact, the description is of the sequence and the structure, and there is lots of disclosure on

how one would use that to make monoclonal antibodies that are agonistic and how to verify that these antibodies are agonistic and how to make monoclonal antibodies to them that are antagonistic.

This disclosure is fully in compliance with paragraph one for enablement purposes and certainly Noelle v Lederman which controls written description for antibodies. In fact, Noelle v Lederman is a case that dealt with an antibody to a receptor, a CD40 receptor. And, if you look at the count in Lederman, there was a function in it, and the function had to do with the fact that this antibody in the Lederman case inhibited the bonding of CD40 receptor to CD40. So, it was an antagonistic antibody.

And I bring the board's attention to the case of Capon v Eshhar, which we have briefed. And in Capon v Eshhar at -- and I cite 418 F3d ~~fifth~~ ~~third~~ 1360. In Capon v Eshhar, the CAFC ~~CFC~~ acknowledged that in doing written description for generic claims and biotechnology ~~by technology~~ it is quite all right

under 112 first paragraph to include experimental verification, even if the concept that is -- that is claimed and claimed to be novel has some variability.

So, the fact that -- as our opponents have pointed out, there are two counts that -- differ~~ent~~ in function that are in some way that have what it -- what they have in common is the structure of this antigen is not fatal to this -- to a ~~termination~~ determination that we have ~~a~~ fully described with a test -- with a step of verification to see whether out of a class of monoclonals that have been made which ones are agonists and which ones are antagonists to comply with 112 first.

So, our position is that these two counts can be fully described under 112 paragraph -- 112 first written description requirements under Noelle, which controls antibody written description 112 first, and Capon. Now --

JUDGE SPIEGEL: Excuse me. Now, if I understand you correctly, then your position is that the disclosure in the applications that

you're requesting benefit of is sufficient to make it obvious to obtain the subject matter of both counts --

MR. GOLDSTEIN: No -- I'm sorry.

JUDGE SPIEGEL: -- that there is not an actual anticipatory description in any of those applications of the subject matter of either count; is that correct?

MR. GOLDSTEIN: No, Your Honor. And I beg to differ respectfully. There is, in fact, an anticipatory description. There is a prophetic constructive reduction to practice description which --

JUDGE SPIEGEL: Would you point me to that please?

MR. GOLDSTEIN: Sure. I would be happy to. I don't have the first ~~party~~ PRIORITY document in front of me, but I can find it for you, and I promise I'll get back to --

JUDGE SPIEGEL: How about if we give you two extra minutes at the end of your rebuttal?

MR. GOLDSTEIN: I will give you page and

line as to where antibodies are fully described. Now, there is no --

JUDGE SPIEGEL: The subject matter of the count --

MR. GOLDSTEIN: Yes.

JUDGE SPIEGEL: -- not a piece here and a piece there?

MR. GOLDSTEIN: Yes. The subject matter of the count is in -- is in our priority document; and, while there is no actual reduction to practice of an antibody in this April 6 patent application, that is by no means ~~failed~~ fatal. I bring the ~~board's~~ Board's attention to the very recent case of Falkner v Inglis, which is slip opinion ~~051324~~ 05-1324 decided in May of 2006.

~~Faulkner~~ Falkner is a case from the ~~federal circuit~~ Federal Circuit dealing with pox viruses and herpes viruses. And in ~~Faulkner~~ Falkner the ~~federal circuit~~ Federal Circuit indicated very clearly that you don't need to have an actual reduction in practice in order to comply with 112 first paragraph in the description.

JUDGE SPIEGEL: So, what you're saying is

that in your earlier applications you have a constructive description of a monoclonal antibody that specifically binds to the DR5 --

MR. GOLDSTEIN: Yes.

JUDGE SPIEGEL: -- as identified by --

JUDGE SCHAFER: As I remember, all of your -- all of your prior documents do describe the DR5 sequence --

MR. GOLDSTEIN: Yes.

JUDGE SCHAFER: -- is that correct?

MR. GOLDSTEIN: And -- and yes, and the domains, correct.

JUDGE SCHAFER: The sequence that's in the count is --

MR. GOLDSTEIN: Yes, Your Honor. So, we have a constructive reduction of practice. Now, what does -- what does Party Adams say about this? They -- their position ultimately comes down to the fact that because in their 119 case they have actually made an antibody, this 3F11 antibody, that you need to have an actual reduction to practice.

Now, this is contradicted by positions that they took earlier on when in this parallel ~~priority~~ prosecution they were trying to get allowance for involved claims essentially to these antibodies. They had a 131 affidavit by their inventor, Dr. Ashkenazi -- and I bring your attention to tab three of my demonstrative exhibits where at paragraphs six and nine of his 131 affidavit Dr. Ashkenazi says that the 216 application, which is an identical application filed on the same day as the 615, he had full conception and constructive reduction to practice of an antibody, an agonistic antibody.

It was not until the 119 case that they actually made one, but early on before this interference was declared Ashkenazi was very happy to swear under oath that he had a constructive reduction to practice. They changed their tune after they realized that perhaps they could make an argument that they had made one here, even though -- not earlier and we hadn't made one until later, but that's only an argument of convenience.

The other thing that contradicts this actual reduction to practice theory of our opponents in addition to ~~Faulkner~~ Falkner is that -- and I bring the ~~board's~~ Board's attention to tab five. This is a portion of the cross-examination of their expert, Dr. Karin, in which Dr. Karin applied his extrinsic post-interference definition and count construction of what an agonist is and what an antagonist is, which contradicts the intrinsic definitions in the specs of the parties.

But, again, because of convenience, Karin defines an agonist as necessarily being limited to a molecule that competes with a ~~cognant~~ cognate ligand and that you need to know the ~~cognant~~ cognate ligand and you need to mimic physiologically relevant conditions. And, with this definition I asked him -- after I took him through the Genentech priority documents -- does Genentech have an agonist antibody, are they entitled to call their antibody an agonist antibody? And he said -- and you can read it right here. He said no.

This is part of our request to file a

supplemental opposition, Your Honor. And you -- if I may refresh your memory, you said that we would address this ~~as~~ at oral hearing.

JUDGE SCHAFER: Yes.

MR. GOLDSTEIN: We believe that during the cross-examination of their expert, there's highly-relevant testimony that came up that concerns their view that they have an actual reduction to practice. Well, it turns out under this post-interference definition of Genentech and Dr. Karin they don't -- and Karin's own testimony they don't have an actual reduction to practice.

So, where does that leave the parties? Well, as far as Genentech is concerned, Karin's testimony says that they don't have an actual reduction to practice here, and they have requested benefit for their '615 application sort of in a piggyback way, saying, if you give it to us [HGS] give it to them [Genentech] too.

And, if you read it, you will see that they don't have a prima ~~facia~~ facie case. In fact, Dr. Karin testified just like Dr. Reed testified

that if you want to know whether you've got an agonist antibody, you just test it. And that is, in fact, found at tab four, page two where I asked Dr. Karin on cross whether if you made a set of monoclonal antibodies and you wanted to know which ones were agonist and which ones were antagonist wouldn't you just test them.

And he said, if that's what you want. And I said, a person of skill in '97 would have done that, too, right. And he said, I believe so. So, the fact that we didn't have a reduction -- an actual reduction to practice does not, in any way, detract from the fact that ~~he~~ we fully enabled, described and provided a credible utility for the production and verification of agonistic and antagonistic antibodies.

JUDGE SPIEGEL: Let me stop you one second here. So, you don't have an actual reduction to practice set forth in those earlier applications? Do you have an anticipatory constructive reduction --

MR. GOLDSTEIN: Yes, I do, Your Honor.

JUDGE SPIEGEL: And that's what you're going to give me?

MR. GOLDSTEIN: Yes.

JUDGE SPIEGEL: Okay. And, if we were to decide to allow the supplemental response, does that mean you are -- you would be withdrawing your motion to exclude from evidence the Karin cross-examination?

MR. GOLDSTEIN: No. I have not moved to exclude from evidence the Karin cross-examination. I have moved to exclude from evidence the Karin redirect examination, not the cross-examination. The redirect examination of Dr. Karin was chock full of leading questions to which we object --

JUDGE SPIEGEL: Yes or no is fine because you're coming up on your time --

MR. GOLDSTEIN: I'm sorry?

JUDGE SPIEGEL: Yes or no is fine.

MR. GOLDSTEIN: Okay, okay. I believe I may have another minute or two. I wanted to raise one last point about this parallel prosecution. We have filed a motion for sanctions against

Genentech on the basis that on May 15th they filed identical patent applications. On February 9, 1998, they filed identical patent applications. They use the '746 patent application, which is this middle purple box when they have claims that where -- involved in the -- that -- there are claims that are involved that correspond to the count.

The examiner in their middle case here was Claire Kaufman. It was the same examiner that was examining our '009 patent application, and they submitted a series of -- essentially what amounted to pre-~~ground~~ grant oppositions against our case in their own case essentially protesting the allowance and issuance of any claim --

JUDGE ~~SPIEGEL~~ SCHAFER: Okay. Assuming all of that stuff you say is true --

MR. GOLDSTEIN: Yes.

JUDGE SCHAFER: -- and we assume that, why do we have jurisdiction to sanction somebody for something that was done in a proceeding that was not before us?

MR. GOLDSTEIN: Well, the ~~board~~ Board has jurisdiction over actions that have occurred ex parte in claims that involved in this interference --

JUDGE ~~SPIEGEL~~ SCHAFER: Why do you we have jurisdiction --

MR. GOLDSTEIN: Well, for example -- the board took jurisdiction, for example, in Norton v Curtis and Langer v. Kaufman and in other cases where inequitable procurement, for example, was committed ex parte in a case that led to an interference, and the ~~board~~ Board then took jurisdiction and was able to decide or not to decide on sanctions.

But these are clearly claims of Genentech that were involved. They, in fact, admitted -- and I have a demo exhibit that -- that the claims were to the same subject matter. When our case was allowed by Examiner Kaufman and they were following this on PAIR, they filed in '05 another protest, another complaint. The main point here that they were trying to accomplish was to prevent

HGS from getting a patent. They wanted the patent first, but do they ever request an interference? Did they ever use rule 202? No.

The only thing they wanted in filing these papers in their own case was to prevent us from getting a patent, and I don't think that the Board ~~board~~ should avoid taking jurisdiction over this and I don't think that the Board ~~board~~ should condone this behavior.

It is, in fact, inappropriate behavior, and it's important to the bar that you send a very strong signal because this sort of thing happens all the time. Not what Genentech has done, but the fact that people follow their competitors' patent applications now on PAIR and realize what's going on and when allowances come out, the temptation to file these papers quote in your own case when you know that it's the same examiner is very high.

JUDGE SCHAFER: Well, what would be the effect -- what if they just said, hey, we know about this application pending; we can see the

spec; we see there's some information that might be relevant; and, here's our 131 affidavit to show that what we did and what we claim we did before?

MR. GOLDSTEIN: Well, Judge Schafer, with all due respect --

JUDGE SPIEGEL: Is that what we have here or is that --

MR. GOLDSTEIN: No.

JUDGE SPIEGEL: -- or is it beyond that?

MR. GOLDSTEIN: Beyond that.

JUDGE SCHAFER: So, it's not just saying we -- in your view, it's not just --

MR. GOLDSTEIN: That's correct.

JUDGE SCHAFER: -- we did this invention earlier, Examiner, so this should never come up as an issue against us, but because we're anticipating --

MR. GOLDSTEIN: This was not just an in re Wertheim ~~regard hand~~ discussion (sic), and it was not a 131. There was a January 2003 so-called 131, which, if you look at it, is not a 131. It's a -- it's a 22-paragraph so-called 131 that has nothing

but attacks on enablement, written description and utility of our case.

JUDGE SCHAFER: Well, wouldn't it be -- isn't it fair, though, when you say this could be a potential reference because -- and I'm going to tell you why this is isn't -- why this isn't a reference for me. Because they have an earlier document, which they need the date of it, and it does not enable the invention that I -- you can give a 102, a 102(b) reference -- looks like a 102(b), and you can show evidence that it really doesn't enable the -- the subject matter relied on in the reference really isn't an enablement and then put in proofs and affidavits to that effect?

MR. GOLDSTEIN: Right.

JUDGE SCHAFER: Can -- can't you do that in the context of 131? I think that might be a misnomer under that circumstance. That would really be, I think, a 132 technically or 132 affidavit. But wouldn't that be an appropriate attack to say, here's this disclosure, it's not enabled so they can't have that date?

MR. GOLDSTEIN: And you would allow them to do this three times, and you would allow them to keep looking at --

JUDGE SCHAFER: I guess the examiner apparently -- well, the examiner never relied on it, right?

MR. GOLDSTEIN: Well, we don't know what --

JUDGE SCHAFER: The problem is that the examiner never said there's a provisional rejection outlaying out here --

MR. GOLDSTEIN: No. That's not the problem. The problem is that they did this in January of '03, in February of '03 and in suspended prosecution in February of '05. There was no reason to do this multiple times. They'd done it once. Even if they wanted to comply with ~~rule~~ Rule 56, they'd already done it. How many times do you have to comply with ~~rule~~ Rule 56? Thank you, Your Honor.

JUDGE SPIEGEL: Thank you. Thank you, sir. Mr. Ashe, will you be reserving rebuttal?

MR. ASHE: Yes, I'd like to reserve five minutes, if I could.

JUDGE SPIEGEL: No. There's no problem if you'd like to discuss two and three together.

MR. ASHE: Okay. And may I approach the bench?

JUDGE SPIEGEL: Yes.

MR. ASHE: Here's three copies and one original, and those have been served on opposing counsel.

JUDGE SCHAFER: Thank you.

MR. ASHE: May it please the board, was your comment you wanted me to address motions two and three? Or may I just --

JUDGE SPIEGEL: Two and three may be addressed together.

MR. ASHE: Okay. What I'd like to do is --

JUDGE SPIEGEL: But whatever order you like.

MR. ASHE: Thank you, Your Honor. I'd like to start off by saying that a lot of issues

have been raised in this interference, and we think that one of the central issues that will determine ~~drag~~ the outcome of the interference is the motion that has been addressed by HGS in their presentation today, and that's mainly HGS motion number three.

And the reason we think that's important is because HGS is Junior Party by a full two years in this interference; and, in their priority statement, they did not allege a date for an actual reduction to practice.

Therefore, their priority case hinges on their benefit position, and their position is that in order to be accorded benefit of these numerous earlier-filed applications, Board Rule ~~board rule~~ 201 says that they have to establish that each of those is a constructive reduction to practice, and that is a described and enabled anticipation of the invention.

And our position is that they have not satisfied that burden of proof. And I don't want to steal the thunder from Mr. Goldstein pointing

to the points in the 846 application where he discloses the antibody, but I'll tell you now it's not there. In the 846 application, there is no description of an antibody in terms of structure, formula, a chemical name, a deposit, any sort of correlation between structure or function. It simply is not there, and these are the well-established hallmarks that you look for for adequate written description and --

JUDGE SPIEGEL: So, would you say that there is an obviousness-type description there, given the disclosure would have been obvious to make the subject matter of the counts rather than an anticipatory disclosure?

MR. ASHE: Right. We -- first of all, we --

JUDGE SPIEGEL ~~SCHAFER~~: Is that your position?

MR. ASHE: Our position, number one, is that the rule requires an anticipatory disclosure. Number two, if it was, in fact, an obviousness disclosure, that would not be sufficient to satisfy written description. And, number three,

we would not agree that the 846 would provide sufficient disclosure to make an obviousness determination. And that really goes into the second part of what they're asking us to look at, the structure that they're asking us to look at, and that is the structure of the antigen itself.

With regard to the case law, they've placed a lot of emphasis on the Noelle v Lederman, and we believe that that case does not get HGS where they need to be in order to be accorded benefit of these earlier filed applications. The case -- the Noelle case dealt with a claim in the discussion -- in Noelle that dealt with this point.

The claim was to any antibody capable of binding to antigen X. And, as we can see in Adams Demonstrative Exhibit No. 1, the counts that are involved in this interference are quite different from that claim that was addressed in the Noelle v Lederman decision. In particular, although each count has an introductory section that talks about the antibody binding to a DR -- extracellular

domain of DR5, each count also has an additional functional recitation.

And, therefore, if you applied the rationale from Noelle and say, okay, they are entitled to claim their antibody based on its ability to bind the DR5 receptor, that description alone, that correlation between structure and function, is still not sufficient to distinguish between the antagonist antibody of Count ~~count~~ one and the agonist antibody of Count ~~count~~ two.

And we believe on that basis that the Noelle decision just does not get them there. They have not explained any rationale that would justify extending Noelle in such a way that they can then point to the 846 and tell you how it satisfies the written description requirement. As Judge Schafer pointed out, this is a problem of written description that runs throughout their entire chain of applications that they are seeking benefit for. This is not a problem that goes away for them.

What I'd like to point to is -- next is

what they actually did present as their invention in the 846 application and in demonstrative number five in the book, which I'll also put up as ~~is~~ a poster board. This is a computer printout of a sequence homology. This is their evidence of the invention for the subject matter of Count ~~count~~ one and Count ~~count~~ two. And from this they say that anybody of ordinary skill in the art could get from this structure to an antibody and that they've described it in such a way that they can satisfy the written description requirements.

We think that that argument is woefully inadequate. If you -- essentially what they've done here is they have taken this -- the lower protein described here is the DR5 sequence, and then they've compared it to three other TNF receptors which they describe as death receptors. And, if you ask Dr. Reed, who is HGS's expert supporting their motion number three, what does all of this mean.

And he'll tell you, well, a death receptor induces apoptosis, and I'm looking at

this homology and you know what? It looks like a death receptor; therefore, DR5 induces apoptosis because death receptors induce apoptosis. And the example he points to is the Fas protein, another TNF receptor. It's the TNF receptor that contains a death domain. And he says, that's it, you're good to go, and all you need for the antibodies now is to do a routine screening. What Dr. Reed --

JUDGE SCHAFER: DR5 -- they did describe the DR5 sequence in their priority?

MR. ASHE: They did, yes --

JUDGE SCHAFER: Did they say it was a death receptor?

MR. ASHE: They said that it was a death receptor, and our position is --

JUDGE SCHAFER: That no one would believe that?

MR. ASHE: -- that no one would believe that. And for good reason. That's not the story that you would get from Dr. Reed. And an interesting thing we need to keep in mind with

regard to Dr. Reed is that his testimony regarding the subject matter of apoptosis was called into question by a court up in -- I believe it was New Jersey or Delaware where he submitted an extensive expert report. And, when that was subjected to scrutiny, it turned out that the only information that he presented was the information that was in favor of his client and the report was thrown out.

Here, we have a similar situation. As I said, he says, you know, Fas, that's a death receptor; therefore, all death receptors do apoptosis and you're good to go. What you hear from Dr. Karin is actually the complete story, and that is that if you go to DR3, which is also a TNF receptor with a death domain, at the time of HGS's filing, it wasn't clear what the function of that was, even though it was a TNF receptor. It had a death domain. They didn't know if it induced apoptosis all the time or whether they knew that it had diverse biological activities.

And the exact same story with the next receptor up there, TNFR1. And, in fact, I direct

your attention to the HGS specification where they recognize -- and this is at, I believe, tabs -- beginning at tab six of the bench book. They give a brief explanation as to the TNF molecules and the fact that there is a TNF ligand superfamily and a TNF receptor superfamily. And then they immediately note that the receptors are varied and influence numerous functions, both normal and abnormal, in the biological processes of the mammalian system.

Specifically, with regard to TNFR1, which Dr. Reed doesn't spend any time talking about, they acknowledge -- and this is at tab 12 of the bench book -- while the central role of Fas is to trigger cell death, TNFR1 can signal an array of diverse biological activities, many of which stem from its ability to activate NF Kappa B ~~sappa V~~.

There's yet another one, another TNF receptor, that contains a death domain that's not in this comparison chart and, again, goes to disprove their theory that based on structure alone one of ordinary skill in the art would look

at the structure and say, this is what this receptor is going to do. That fourth example is P75NGFR. Again, a TNF receptor. It contains a death domain. When the ~~cognant~~ cognate ligand binds to that, it actually has an anti-apoptotic effect.

JUDGE SPIEGEL: So, your position is if one of ordinary skill in the art does not know that this is, in fact, a death receptor, then, although given the amino acid sequence of the receptor protein, one would not know now how to screen for it?

MR. ASHE: No. My position is even if they knew that it was a death receptor, and death receptor is based on a structural -- it is a structural definition. If I could actually on that point -- perhaps this will explain it --

JUDGE SPIEGEL: Essentially, it's an antibody that specifically binds to this protein, and we have the description of the protein.

MR. ASHE: That's correct, but you don't have the antibody. Nowhere in their specification do they --

JUDGE SPIEGEL: We don't -- we don't have the antibody?

MR. ASHE: Correct.

JUDGE SPIEGEL: But the other part of each count is the antibody is either agonist or antagonist?

MR. ASHE: That's correct. So, if I could just add -- if one of ordinary skill in the art looked at that and he said, I have this new receptor, it's DR5; and, based on ~~sequence,~~ sequence similarity, homology, we're going to call it a death receptor. It's a TNF receptor, and it also has a death domain and that equals the structural definition of a death receptor, and I have an agonist antibody for this.

One of ordinary skill in the art is going to say, that's very interesting, what does it do, what do you mean by agonist. Because these have diverse biological activities, even though they're called death receptors.

And that is the entire body of literature that Dr. Reed did not address. He spent the first

32 paragraphs of his declaration talking about his credentials, 600 publications in this area, hottest scientist of the year. He doesn't spend any time talking about the multiple functions of TNFR. He doesn't spend any time talking about DR3. He doesn't spend any time talking about P75NGFR. And why not? Because that completely goes against his theory that a death receptor induces apoptosis.

So, we think -- our position is that one of ordinary skill in the art looking at the sequence comparison would say, this is a great start, but now we need to do the experiments. And that's what you saw in Noelle. That's the second distinguishing factor about Noelle. Noelle wasn't dealing with a computer printout of a sequence comparison. He was dealing with CD40CR, CD40, both well-characterized proteins. They are characterized by actual experiments described in the specifications. So, it's not an applicable case and that's our position.

With regard to -- let me just -- so, our

position in conclusion is that, with regard to their motion for benefit of these earlier-filed applications, they're required to show that there's an anticipatory and enabled disclosure and an anticipatory disclosure. That means it's got to be there. If you look to the spec, you do not find anything with regard to antibody structure, a deposit or anything like that. This is where they leave you and, from this point on, it's a research plan.

Another point of their argument weighs heavily on the enablement. And they say, we enabled this invention; all you have to do with our 846 is take the sequence and go. The problem is all of the ~~ELISA assay~~ assays that they describe require knowledge of the ~~cognant~~ cognate ligand, and they don't disclose that. That wasn't disclosed until their July '97 application; and, therefore, they don't provide you with the tools. It's a research plan again.

If you ask them the day that they filed the application what's the ligand, they would say,

what ligand, what are you talking about, we don't know what it is. We can tell you what TNF ligands were out there, but we don't know which one is for this receptor. So, how do you test to see whether it's an agonist or an antagonist without that information? They don't tell you. Another fundamental problem with their case --

JUDGE SPIEGEL: Would you mind spending some time discussing your monoclonal antibody that goes by the 3F11 period 39 period seven please? In particular, I'm interested in the apparently inconsistent descriptions in your specification of the 119 application --

MR. ASHE: Yes.

JUDGE SPIEGEL: -- where on page 47 at lines 20 to 36 you're stating that this monoclonal antibody is characterized as having agonistic activity for inducing apoptosis while on page -- the next page on page 67, lines 26 to 36 that paragraph concludes accordingly it is believed that the 3F11 period 39 period seven antibody is a blocking enable to antibody, which would make it

an antagonist --

MR. ASHE: Correct.

JUDGE SPIEGEL: -- because it's blocking. So, how can -- two questions. First, how can the same antibody be both an agonist as well as an antagonist? And, secondly -- because the subject matter of the count requires the monoclonal antibodies specifically bind to a receptor. On page 47 in that paragraph, lines 20 to 36, it talks about this particular monoclonal antibody being cross-reactive to DR4. So, if that monoclonal is cross-reactive with DR4, how can it be an antibody that specifically binds to DR5?

So, two questions: How can it both agonist and antagonist, and where in your specification does it tell me that something which cross-reacts with another receptor specifically binds DR5?

MR. ASHE: Okay. If I could just, for discussion purposes, refer to it as 3F11?

JUDGE SPIEGEL: Sure.

MR. KENEHAN: Okay. With regard to the

first question, how could it be both agonist and antagonist, in this specification the inventors took this candidate antibody, and they introduced it into a cellular model where they had the appropriate controls and they observed apoptosis. As another control, they had the same cell line. They introduced the apo2 ligand, which is the cognate ~~cognant~~ ligand for this receptor.

They observed apoptosis. The antibody they were using, 3F11, was shown in the examples to bind to the extracellular domain of DR5. They observed apoptosis. They concluded this is an apoptosis-inducing antibody and, therefore, in the context of knowing the ligand, they can call it an agonist.

And they also conducted additional experiments where they have the antibody. They observed apoptosis. With that same experiment, you can have the antibody and also have present in that system the cognate ~~cognant~~ ligand. And what they observed is that the amount of apoptosis that you observed in that instance was less than what you

would observe if you only had the ~~cognant~~ cognate ligand present. And their conclusion was that the 3F11 antibody was blocking the ~~cognant~~ cognate ligand from actually binding and having its full effect. So, in that sense, it is blocking the ligand receptor. It's an antagonist antibody. With regard to your question --

JUDGE SPIEGEL: Well, just one second. Based on that -- on that disclosure, how is one -- how is the public to decide whether they've got an agonist or an antagonist antibody?

MR. ASHE: That's the critical feature that I was pointing to that was missing from the 846 application. If you have the ~~cognant~~ cognate ligand and you're able to assess what happens upon ~~cognant~~ cognate ligand binding, you can --

JUDGE SPIEGEL: But there's nothing in the subject matter of counts that say it's an agonist or an antagonist in the presence of the ~~cognant~~ cognate ligand. That's not a limitation of the count.

MR. ASHE: But in order to impart meaning

to the term agonist and antagonist, you have to know what the ~~cognant~~ cognate ligand is. So, I would say if the express term is not in the count -- which you're correct, it's not -- that is what is understood by one of ordinary skill in the art, and this is the testimony which HGS --

JUDGE SPIEGEL: So, if that's the case, then you're saying that ~~3F~~ SFII is a blocking or antagonist. It is not an agonist.

MR. ASHE: No. But it's an agonist because it can induce apoptosis by itself without anything else being present. So, it acts as an agonist.

JUDGE SCHAFER: So, what you're saying is that when it's there by itself, if things go along like you expect -- but if you put in the normal stuff that causes the apoptosis, it blocks it and slows it down so in that case --

MR. ASHE: Yes.

JUDGE SCHAFER: -- alive and dead at the same time.

MR. ASHE: I think one way of looking at

it -- one way of looking at it is you can have an antagonist antibody that completely blocks the ligand. You can have an agonist that causes the apoptotic effect. The 3F11 antibody is special in the sense -- and that's why it's called blocking antibody -- because it's able to block the ligand from binding as well as it does have an agonist -- so, we believe that it satisfies both counts and that's why we move for benefit.

And, again, I think the issue here is we have, in fact, described an actual antibody and that's in contrast to the HGS applications, something that's missing so --

JUDGE SPIEGEL: And getting on to cross-reactivity --

MR. ASHE: Yes. There is that passage that talks about cross-reactivity with DR4, and I believe the appropriate figure to look at with regard to that is figure 11, which is at the end of the -- my copy of the specification. And basically what this is, ~~is~~ it's an ELISA assay that shows the amount of ~~about~~ absorbance with the

antibody binding to DR5 here, and then you have control antibody -- or control antigens down here. And as you can see the -- is the -- there is a significant difference between the binding of the 3F11 antibody to DR5 compared to the controls and only at these very high concentrations do you see cross-reactivity.

I think this question, though, is significant, again, looking back to the sufficiency of the 846 application because just having the antibody isn't enough if you don't know how to screen for it, and you don't now how to control for things such as cross-reactivity and you don't know the ligands. That's really the problem that they don't overcome in explaining how their 846 application is enabling, let alone the failure to describe any antibody.

JUDGE SPIEGEL: Okay, okay. When it's time for you to do your rebuttal, if you would kindly let me know where in the application it defines specific binding to allow for this cross-reactively with DR4, I would really

appreciate that.

In the few minutes you have left, would you please address your first motion to correspond additional claims to count two.

MR. ASHE: Sure. That motion was filed after we observed that the interference as declared had the antagonist count, the agonist count. The claims that were designated as corresponding to the antagonist count included the antagonist claims as well as a generic set of claims, and they're generic in the sense that they do not recite either agonist or antagonist. And, based on that observation, it appeared that those generic claims should also be designated as corresponding to count two, which is the agonist count --

JUDGE SCHAFER: The reason is they anticipate --

MR. ASHE: That's correct.

JUDGE SCHAFER: -- probably some anticipate, but --

MR. ASHE: So, our --

JUDGE SCHAFER: That's your position?

MR. ASHE: That's it. And --

JUDGE SPIEGEL: And so, it should be -- they should be -- they should correspond.

MR. ASHE: That's our position. That's correct, yes. And, if there are no further questions, I'd just like to summarize again --

JUDGE SPIEGEL: Wait. I'm sorry, but where in your motion did you state which generic claims were anticipated by the subject matter of count two and where was your obviousness analysis?

MR. ASHE: What we relied upon was the original structure of the counts ~~in~~ and the original designation of claims. We do not have an obviousness argument included. Our position is that for the same reasons an antagonistic claim would anticipate or render obvious these generic claims, an agonist antibody would do the same.

JUDGE SPIEGEL: But you didn't set forth those reasons?

MR. ASHE: We set it forth in those terms, but we did not go claim by claim and --

JUDGE SCHAFER: Let me ask you -- the claims that you want to designate to correspond to count two, are they anticipated?

MR. ASHE: We believe they're either anticipated or rendered obvious by -- and that's -- by applying the rationale upon which that motion was filed, we believe that that's the case. One other -- the -- board number three. Could I make one last point before I --

JUDGE SPIEGEL: Go into rebuttal?

MR. ASHE: One thing that I would like to point out is a procedural note with regard to the motion for benefit of HGS, and that is -- board rule 201 not only requires that you establish a constructive reduction to practice, it further requires that you show that that construction reduction to practice -- for your earliest constructive reduction to practice -- is continuously disclosed throughout the chain of applications.

And here, as a procedural matter, I think that they failed to do that. Their entire motion focuses on the 846 and the 021, but there's

absolutely no mention either with claim charts ~~parts~~ or any other evidence that these other applications would also constitute a constructive reduction to practice, including their involved patent, which is the requirement of the rule.

It's significant here because, number one, you have a bunch of provisional applications, and there's no telling how the disclosures changed from one to the other.

And then finally you have a CIP here, and there is, if you compare to the two documents, a significant difference between their issued patent, the disclosure that's in there, and what you see in the 846 application. So, I just want to point out as a procedural matter they really -- you know, they don't cover any of this in their motion and they were supposed to do that. Thank you.

JUDGE SPIEGEL: Mr. Goldstein, rebuttal please.

MR. GOLDSTEIN: Thank you, Your Honor. Can I take the two minutes you gave me?

JUDGE SPIEGEL: Anything left over you get to keep for rebuttal.

MR. GOLDSTEIN: Well, first of all, we did describe where the invention is constructively ~~constructive~~ reduced practice in all the other -- in all of the other patent applications at page 23 of our motion. At page 27 -- and now I'm going to talk about the 846 patent application. Page 27, line 18 agonists are discussed; antagonists are discussed. Page 29, line 20 antagonist antibodies are discussed. At page 29, line 14 we say further preferred ~~prefer~~ agonist include polyclonal and monoclonal antibodies raised against the DR5 polypeptide or a fragment thereof. Page 27, line 16 we talk about antagonists, including against soluble forms of DR5 and monoclonal antibodies directed against the DR5 polypeptide. Those are just a few specific examples where we mention antagonist and agonist antibodies.

Counsel for Genentech is distinguishing Noelle on what is not a real distinction. In fact, he misrepresented the claims that were

involved in Noelle. The Lederman claim in Noelle which was part of the McKelvey ~~McCaulley~~ count had function in it. It, in fact, was not just an ~~a~~ antibody that binds the CD40 receptor, but, in fact, it says further that it is an antibody that inhibits the binding of the receptor to the ligand. That is an antagonistic antibody.

And it is not just Noelle, but Noelle, which had function in the -- in the count, and Capon, which says that for generic claims in 112 first paragraph written description requirements, it's okay to have some screening ~~subscreening~~ and some variability in the generic concept that is patentable. So, the distinction that they're making about Noelle is one without a difference.

And now let me talk a little bit about Dr. Reed. I think it is unfair for Party Adams to come into oral hearing and talk about how Reed was criticized by some judge in a Federal District Court in a case that had nothing to do with an interference, nothing to do with the involved claims, nothing to do with Trail R2, with DR5. It had to

do with something entirely different when -- they did not cross-examine Dr. Reed. They chose voluntarily not to cross-examine him, and this was the time for them to ask him and to impeach him and try to elicit from him why it is that some judge in some other case that had nothing to do with this criticized him for not having reviewed other pieces of art.

The reality is, had they asked them, he would have explained that in that case his role was to find literature that supported a particular position, not to do a general survey. But they didn't ask him. So, they shouldn't be heard here to complain that Dr. Reed was critiqued by some judge in a case that has nothing do with it.

Now, Judge Schafer, you asked very, very clearly whether their position is whether one of skill in the art would have believed that the new death receptor, this new molecule that had been discovered by Ni, was credibly a death receptor or not, and they showed you the homology comparisons.

But our case is not based only on

homology comparisons. Our case is based on the fact that this is a TNFR molecule with a death domain, and there were three TNFR molecules with death domains. They may have had slightly different activities, but the thing they had in common -- and, if you look at the literature and if you look at the citations that have been put forth in this case, you would realize the thing that they had in common -- that ~~the~~ DR3, TNFR1 and Fas had in common was apoptosis.

They make a big deal out of this need to understand what the cognate ~~cognant~~ ligand is and that you are not entitled to call something an agonist unless you know what the cognate ~~cognant~~ ligand is. The reality of it is that this is a construction of the word of the count, as I explained earlier, that is not supported in either of the count -- in either of the parties' patent applications.

The intrinsic evidence is pretty clear. An agonist antibody in Genentech's case is defined as one that induces apoptosis; an antagonist is one that inhibits. There's no requirement, as

Judge Spiegel clearly pointed out, that there be a ~~cognant~~ cognate ligand in that definition, and our definition didn't have a ~~cognant~~ cognate ligand either and the count doesn't have a ~~cognant~~ cognate ligand.

So, this is a post-interference ~~so construction~~ count construction that is convenient so that they can argue that they have an actual reduction to practice with this 3F11 antibody, which, frankly, I don't understand either how --

JUDGE SCHAFER: No one apparently thought it was significant enough to include in their claims, and the count is based --

MR. GOLDSTEIN: Exactly.

JUDGE SPIEGEL: -- on the claims of the parties.

MR. GOLDSTEIN: Exactly. And, in fact, during the cross-examination of Dr. Karin, Dr. Karin agreed that the overwhelming majority of the literature and five additional dictionaries -- not -- not the one that he picked, but five additional dictionaries, in fact, define agonists as molecules that induce apoptosis. And there is

no -- or -- or induce the activity, but there's no requirement of this cognate ~~cognant~~ ligand.

Dr. Reed -- by the way, his testimony was also mischaracterized. Dr. Reed disclosed P75 at paragraph 17. He discussed TNFR1 at paragraph 29 of his declaration, which is Exhibit 2064. He discussed TNFRs generally at 17 to 20.

And, last, they say all the assays ~~assets~~ that we describe in the patent application Require ~~requires~~ a cognate ~~cognant~~ ligand. That is not the case. Example five, which is -- which is an example that was present in the original case in a prophetic manner and was an actual example in the second priority document, in fact, shows that with a standard apoptosis assay Dr. Reed, looking at that example, testified -- and, again, they didn't cross-examine him -- that -- that anybody would be able to test whether an antibody was agonist or antagonistic using that assay.

In sum, we believe that our 846 priority document enables, describes agonistic and antagonistic antibodies and that the utility is

credible to one of ordinary skill in the art. There is no question that the utility, as predicted, was accurate and, in fact, demonstrated by lots of subsequent experimentation and papers that this was, in fact, a death receptor.

So, I don't think that the Board ~~board~~ should agree with their view or their proposed view that one of skill would not have believed that this is a death receptor. This isn't just homology. This is a whole structure plus homology plus well-established apoptotic death receptors in the prior art.

JUDGE SPIEGEL: Thank you, sir.

MR. GOLDSTEIN: Thank you.

JUDGE SPIEGEL: Mr. Ashe.

MR. ASHE: Thank you. Now, I would like to respond to a few comments that Mr. Goldstein made as well as your question regarding the specificity. First, what I'd like to point out is in the comments where they were explaining their position on motion four, they described their conception as something that would encompass any

death receptor discovered in the future, any antibody that bound to it. We think that's clearly not what you need for a conception of a composition. It's very clear.

And I think what you have in figure two, which is put into their 846 application, is the product of that type of thinking. This doesn't get you any further than what a computer has printed out for them. And they cannot, based on this, send the public off on a research plan to come up with the antibodies that they now want to claim.

That's not the way the patent system works. The patent system is very clear. If you are in possession of something, describe it. That's all they ask you to do it. So, if you're in possession of an antibody, describe it in some meaningful way. And I don't think that that principle is overturned or really in any way altered by Noelle.

Noelle says that you need to correlate structure with function. It's the same type of

language that we saw in -- it's the language that you see in the guidelines. And the rationale that was expressed in Noelle was directed very specifically -- and I have it set forth in my bench book -- to the situation where you were claiming any antibody capable of binding to antigen X. That was what was in quotes.

And the board in the federal circuit never reached really the issue of what was adequate or not with regard to the disclosure in Noelle because they found that they didn't have the underlying antigen disclosed. That's where Noelle ended, and they focused, again, in commentary on this passage from the written description requirements.

But if you apply the rationale of Noelle, it does not provide a basis for describing the subject matter in count one or count two, and HGS, although they rely on that single passage from that case, do not explain how it actually provides sufficient -- would provide a rationale for written description that is in accordance with the

well-established law and how their specification would comply with that new rationale.

So, we think that our position on Noelle is the right one, and I think that they have failed throughout all of their applications to disclose any antibody, and the proof positive of this is in their priority statement. They don't allege a day for an actual reduction to practice. So, in the record of this interference, as we sit here today, they still don't have it.

With regard to the question regarding specificity, again, I'd like to direct the board's attention to figure 11, which I pointed out before, this is the ELISA, and I think that this does show a high degree of separation with regard to the binding of 3F11, the DR5 receptor and as far as --

JUDGE SPIEGEL: Hold on. I'm sorry. You said that the subject matter in the count is based on the claim from the 448 application?

MR. ASHE: Yes.

JUDGE SPIEGEL: And that is the

appropriate place to look for the definition --

MR. ASHE: Okay. I believe in the -- I think the specification will be the same and a -- the document that I grabbed is the 119, and I can provide you with a parallel ~~site~~ cite in a minute. But what I can find in the short period of time that I have remaining that relates to the specificity of a monoclonal antibody as it's defined in this application appears on page 14 lines 16, 17 -- 18 to 19 and reads, monoclonal antibodies are highly specific being directed against a single antigenic site. And I believe that the -- the experimental data reflected in figure 11 is consistent with that definition of specificity.

If there are no further questions, I thank you.

JUDGE SPIEGEL: Well, I thank you all for coming. We're going to take the case under advisement, and we would certainly like ~~the~~ to thank the court reporter for being here, for being kind of the silent workhorse that gets very little, if any credit. We do appreciate ~~you're~~ your being here.

With that, we'll take this under advisement.
Thank you.

(WHEREUPON, at 3:11 p.m., the hearing was adjourned.)

- - -

CERTIFICATE OF NOTARY PUBLIC

I, SANDY MEDFORD NELSON, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me in stenotype and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by and the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

SANDY MEDFORD NELSON
Notary Public in and for the
State of Virginia

My commission expires:
September 30, 2010

Court Hearing 7/27/06

Court Hearing 7/27/06

Court Hearing 7/27/06

Court Hearing 7/27/06

Court Hearing 7/27/06

Court Hearing 7/27/06

EXHIBIT F

The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper 139

By: Trial Section Merits Panel
Board of Patent Appeals and Interferences
U.S. Patent and Trademark Office
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Alexandria, VA 22313-1450
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Filed: October 8, 2003

UNITED STATES PATENT AND TRADEMARK OFFICE
(Administrative Patent Judge Carol A. Spiegel)

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

GARY H. RASMUSSON and GLENN F. REYNOLDS

MAILED
OCT 8 2003
PAT & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Junior Party,
Application 08/460,296

v.

SMITHKLINE BEECHAM CORPORATION

Senior Party,
U.S. Patent 5,637,310
U.S. Patent 5,496,556
Reissue Application 09/964,383
Reissue Application 09/984,083

Patent Interference 104,646

Before: SCHAFER, TORCZON and SPIEGEL, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

ORDER VACATING O.C. and ENTERING FINAL JUDGMENT
(37 CFR § 1.658)

A. Conference calls

Two telephone conference calls have been held as a result of the ORDER TO SHOW CAUSE ("O.C.," Paper 138) which issued September 24, 2003.

1. September 30, 2003

A first telephone conference was held on September 30, 2003 at approximately 1:50 p.m., involving:

1. Richard E. Schafer and Carol A. Spiegel, Administrative Patent Judges.
2. Herbert H. Mintz, Esq. and Lara C. Kelley, Esq., counsel for SMITHKLINE BEECHAM CORPORATION (SKB).
3. Daniel S. Glueck, Esq., counsel for RASMUSSON.

The primary purpose of the conference call was to discuss Rasmusson's position vis-a-vis the O.C. (Paper 138). Rasmusson has had the opportunity to and did (a) file preliminary and miscellaneous motions, (b) take testimony in regard thereto, (c) have a hearing on said motions and (d) receive a MEMORANDUM OPINION and ORDER ("Decision," Paper 122) thereon. Rasmusson also had the opportunity to and did (d) request reconsideration of the Order and (e) receive a decision thereon (see DECISION ON RECONSIDERATION and ERRATA (Papers 135 and 136). As confirmed by Mr. Glueck, Rasmusson has chosen not to assert a priority contest. When asked if there was any other matter necessary to decide before proceeding to final judgment, Mr. Glueck replied that Rasmusson could not think of anything else but requested until 12:00 p.m. on October 3, 2003 to bring any unresolved matter to the Board's attention.[1]

In short, there appeared to be no reason to continue the interference proceeding since Rasmusson has chosen not to present evidence on the issue of priority or derivation and Rasmusson has already taken testimony and had a hearing on motions and has received both a decision on motions and a reconsideration thereof by a three-

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[1] According to the O.C. (Paper 138, p. 2), Rasmusson was ordered to "notify the Board of any other matter necessary to resolve the interference within **ten (10) days** of the filing of this order by filing a brief for final hearing in accordance with 37 CFR § 1.656" and to make "any request for a final hearing ... within **ten (10) days** of the filing of this order.

judge panel. It was proposed that the O.C. be vacated, that the Decision and the Decision on Reconsideration be merged into a final judgment and that the hearing on motions be deemed to be a final hearing for purposes of this interference proceeding. It was agreed that a final judgment would issue on October 3, 2003 unless Rasmusson brought any other unresolved matter to the Board's attention via a conference call before 12:00 p.m. on October 3, 2003.

2. October 3, 2003

A second telephone conference call was held on October 3, 2003 at approximately 11:00 a.m., involving:

1. Carol A. Spiegel, Administrative Patent Judge.
2. Herbert H. Mintz, Esq. and Lara C. Kelley, Esq., counsel for SKB.
3. Robert L. Baechtold, Esq. and Daniel S. Glueck, Esq., counsel for Rasmusson. Mr. Haiyan Chen was also present for Rasmusson.

According to Mr. Glueck, the aforementioned proposal was unacceptable to Rasmusson because it felt required to file a final brief and request a final hearing in order to have a "final" decision from the Board for purposes of appeal. Rasmusson stated that it would brief and argue the same issues it had raised in <u>RASMUSSON REQUEST FOR RECONSIDERATION</u> (Paper 127) for "final hearing," in particular the granting of SKB preliminary motion 3 which stripped Rasmusson of the priority benefit of its eight earlier filed applications. In other words, as pointed out by Mr. Mintz, no new issues or arguments would be briefed and argued that had not already been briefed and argued. SKB wondered what justification there was for expending any additional time, effort and money on what has already been decided ("heard") and reconsidered ("reheard"). Neither Rasmusson nor SKB took any position as to priority. The sole concern was whether any judgment which issued after vacating the O.C. could be considered a "final" judgment.

B. This judgment is "final" appealable decision

1. finality is determined pragmatically

Finality is required for judicial review. Barton v. Adang, 162 F.3d 1140, 1143, 49 USPQ2d 1128, 1131 (Fed. Cir. 1998). "For purposes of review, an agency action is final if it (1) represents 'a terminal, complete resolution of the case before the agency,' ... and (2) "determine[s] rights or obligations, or ha[s] some legal consequence" (Capital Network System, Inc. v. F.C.C., 3 F.3d 1526, 1530 (C.A.D.C. 1993) (citations omitted). "To determine whether an agency action is to be deemed 'final' for purposes of judicial review, we look 'in a pragmatic way' to whether the challenged agency action is 'definitive' and to whether it has a 'direct and immediate ... effect on the day-to-day business' of the challenger." Chicago Truck Drivers, Helpers and Warehouse Workers Union (Independent) v. National Mediation Bd., 670 F.2d 665, 668 (C.A. 7 (Ill.) 1981) (citations omitted).

As set forth in Hells Canyon Preservation Council v. Richmond, 841 F.Supp. 1039 (D.Or. 1993):

> [t]he "finality" requirement mandates that a plaintiff identify a "final agency action" and is designed to (1) avoid premature interruption of the administrative process; (2) let the agency develop the necessary factual background upon which decisions should be based; (3) permit the agency to exercise its discretion or apply its expertise; (4) improve the efficiency of the administrative process; (5) conserve scarce judicial resources, since the plaintiff may be successful in vindicating rights in the administrative process and the courts may never have to intervene; (6) give the agency a chance to discover and correct its own errors; and (7) avoid the possibility that flouting of administrative processes could weaken the effectiveness of an agency by encouraging people to ignore its procedures. United States Postal Service v. Notestine, 857 F.2d 989, 993 (5th Cir. 1988) (citations omitted).

2. this action is final for purposes of judicial review

According to 37 CFR § 1.654, "parties will be given an opportunity to appear before the Board to present oral argument at a final hearing" "[a]t an appropriate stage

of the interference." 37 CFR § 1.655 addresses the matters to be considered in rendering a final decision, and reads, in relevant part,

> (a) [i]n rendering a final decision, the Board may consider any properly raised issue, including priority of invention, derivation by an opponent who filed a preliminary statement under § 1.625, patentability of the invention, admissibility of evidence, any interlocutory matter deferred to final hearing, and any other matter necessary to resolve the interference. The Board may also consider whether an interlocutory order should be modified. ... .

a. Rasmusson has chosen not to assert a priority or derivation challenge

The fundamental purpose of an interference is to determine priority. 35 U.S.C. § 102(g). Rasmusson has chosen not to assert a priority or derivation challenge.[2]

b. interlocutory matters have been heard, decided and the decision reconsidered for possible modification

Rasmusson and SKB have received a decision on their remaining preliminary and miscellaneous motions following oral argument by a three judge panel (Paper 122).[3] No motions have been deferred. Under current practice, three judge panel decisions bind further action during the interference proceeding.[4] Cf. 35 U.S.C.

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[2] Rasmusson did not serve evidence on the issue of priority or derivation by time period 2, September 8, 2003 (Paper 132, p. 3). Rasmusson's counsel has confirmed at least twice that Rasmusson will not be filing such evidence (see telephone conferences of September 30 and October 3, 2003).

[3] SKB preliminary motion 1 and miscellaneous motion 1 were denied (Papers 29 and 100, respectively). Rasmusson miscellaneous motions 2 and 3 were denied (Paper 60).

[4] According to the STANDING ORDER governing proceedings before the Trial Section (in relevant part),

> **20. Decisions**
> **20.1 Three-judge decisions govern further proceedings**
> An interlocutory order (37 CFR § 1.601(q)) entered by a panel consisting of three or more administrative patent judges generally governs further proceedings in an interference.
> **20.2. Request for reconsideration**
> **20.2.1** Reconsideration of interlocutory orders
> A party may request reconsideration of any interlocutory order (37 CFR § 1.640(c)).
> A party may request review at final hearing of any interlocutory order (37 CFR §

§ 6(b) (patentability and priority determined by panels of at least three). Rasmusson promptly sought reconsideration of the decision (Paper 127). SKB's views on Rasmusson's request for reconsideration were also "heard" (Paper 133). A decision on reconsideration was issued (Papers 135 and 136).

c. no other issues necessary to resolve the interference exist

Neither Rasmusson nor SKB have been able to identify any other issue which remains to be resolved in this interference.

d. under these circumstances, this action is final for purposes of judicial review

To the extent that current practice may be interpreted as requiring a final hearing with briefing for purposes of "finality," we deem the hearing on motions to be that "final hearing" and note that matters to be addressed at final hearing (37 CFR § 1.658(a)) have been addressed already. Therefore, we merge our prior decisions on motions (Papers 29, 60, 100, 122, 135 and 136) into a "final" decision.

The proceeding is not being prematurely interrupted. Rather, termination of the interference at this point is consistent with securing "the just, speedy, and inexpensive determination" of the interference by avoiding needlessly subjecting the parties to redundant and unnecessary expenditures of time, effort and money. 37 CFR § 1.601. Indeed, there are no issues remaining for us to decide. In other words, the necessary factual background has been fully developed and the Board has exercised its discretion and applied its expertise. Going forward with a final briefing and final hearing where nothing new is being added and priority is not being determined does not improve the efficiency of the administrative process and needlessly expends the resources of the parties and the Board. Moreover, Rasmusson's request for reconsideration has

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1.655(a)), but the panel that will conduct the review generally will be the same panel that entered the interlocutory order even if other issues at final hearing are determined by a separate panel. Accordingly, the most efficient way to seek review of an interlocutory order entered by a panel is through a request for reconsideration.

* * * * * *

20.2.2 Number of requests

No more than one request for reconsideration may be filed per party per board decision.

presented the Board with the chance to discover and correct its own errors. Finally, there is no apparent denial of due process since all issues fairly presented and fully briefed have been decided by a three judge panel after oral hearing on the merits followed by reconsideration of the initial decision.

3. this action is without prejudice to either party requesting a final hearing in the event of remand or reversal by our reviewing court

In the event that a reviewing court reverses and/or remands the merger of our decision on motions and reconsideration thereof into a final action, the parties will not be deemed to have waived their right to a final hearing in accordance with 37 CFR §§ 1.654-1.656. Further, insofar as SKB has taken no position on priority, SKB is deemed not to have waived its right to testimony on the issue of priority.

C. Order

Therefore, in order to secure the just, speedy and inexpensive determination of interference, it is

ORDERED that the ORDER TO SHOW CAUSE issued September 24, 2003 (Paper 138) is vacated.

FURTHER ORDERED that all of the initial decisions on motions, i.e., MEMORANDUM OPINION and ORDER (Papers 29, 60, 100 and 122), DECISION ON RECONSIDERATION (Paper 135) and ERRATA (Paper 136) are merged into this FINAL JUDGMENT.

FURTHER ORDERED that judgment on priority as to Count 2, the sole count in the interference (Paper 123), is awarded against junior party Rasmusson, i.e., GARY H. RASMUSSON and GLENN F. REYNOLDS.

FURTHER ORDERED that junior party Rasmusson, i.e., GARY H. RASMUSSON and GLENN F. REYNOLDS, is not entitled to a patent containing claims 1-8 (corresponding to Count 2) of application 08/460,296, filed June 2, 1995.

FURTHER ORDERED that a copy of this paper shall be made of record in the files of Rasmusson application 08/460,296, of SKB reissue applications 09/964,383 and 09/984,083 and U.S. Patents 5,637,310 and 5,496,556 issued to SKB.

FURTHER ORDERED that if there is a settlement agreement which has not been filed, attention is directed to 35 U.S.C. § 135(c) and 37 CFR § 1.661.

RICHARD E. SCHAFER)
Administrative Patent Judge)

RICHARD TORCZON) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
) INTERFERENCES

CAROL A. SPIEGEL)
Administrative Patent Judge)

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EXHIBIT G

Paper ______

Filed on behalf of : Party Ni
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Richard E. Schafer)

Human Genome Sciences, Inc.
Junior Party
(Patent 6,872,568;
Inventors: Jian Ni, Reiner L. Gentz, Guo-Liang Yu, Craig A. Rosen),

v.

Genentech, Inc.
Senior Party
(Application 10/423,448;
Inventors: Camellia W. Adams, Avi J. Ashkenazi, Anan Chuntharapai, Kyung Jin Kim).

Patent Interference No. 105,361 (RES)

NI EXHIBIT LIST

Ni Exhibit List for Interference No. 105,361

Ni Exhibit #	*Description*
Ni Exhibit 2001	Notice of Interference No. 105,240, dated August 31, 2005
Ni Exhibit 2002	Ni Real Party-in-Interest, filed in Interference 105,240
Ni Exhibit 2003	Rauch Designation of Real Party in Interest, filed in Interference 105,240
Ni Exhibit 2004	Ni U.S. Patent No. 6,872,568
Ni Exhibit 2005	Srivastava, *Neoplasia 3*:535-546 (2001) "TRAIL/Apo-2L: Mechanisms and Clinical Applications in Cancer"
Ni Exhibit 2006	Notice Declaring Interference 105,077
Ni Exhibit 2007	Wiley Notification of Real Party in Interest, filed in Interference 105,077
Ni Exhibit 2008	Wiley Supplemental Notice as to real Party in Interest, filed in Interference 105,077
Ni Exhibit 2009	Wiley U.S. Patent No. 5,763,223
Ni Exhibit 2010	Declaration of Diane L. Marschang, filed in Interference 105,077 as Wiley Exhibit 1067
Ni Exhibit 2011	Excerpt of Transcript of Deposition of Diane Marschang, taken in connection with Interference 105,077
Ni Exhibit 2012	Transcript of Deposition of Carl Ware, filed in Interference 105,077 as Ruben Exhibit 2192
Ni Exhibit 2013	Excerpt of Transcript of Deposition of Steven M. Ruben, taken in connection with Interference 105,077
Ni Exhibit 2014	Excerpt of Transcript of Deposition of Nigel Patrick Killeen, filed in Interference 105,077 as Wiley Exhibit 1097
Ni Exhibit 2015	Huisman *et al.*, *Clinical Cancer Research 8*:596-606 (2002) "Paclitaxel Triggers Cell Death Primarily via Caspase-independent Routes in the Non-Small Cell Lung Cancer Cell Line NCI-H460"
Ni Exhibit 2016	Order-Rule 123(a) (Times for substantive motions; priority deferred), dated August 31, 2005 for Interference 105,240
Ni Exhibit 2017	Excerpt of the public record in Patent Application Information (PAIR) for U.S. Application 10/423,448
Ni Exhibit 2018	Yagita *et al.*, *Cancer Sci. 95*:777-783 (2004) "TRAIL and its receptors as targets for cancer therapy"
Ni Exhibit 2019	Adams U.S. Appl. Publ. No. 2004/0009552 A1
Ni Exhibit 2020	Redacted copy of Material Transfer Agreement (MTA) between Human Genome Sciences and the University of Michigan, and Amendment Nos. 1 to 9 of the MTA
Ni Exhibit 2021	Sheridan *et al.*, *Science 277*:818-821 (August 8, 1997) "Control of TRAIL-induced Apoptosis by a Family of Signaling and Decoy Receptors"

Ni Exhibit #	***Description***
Ni Exhibit 2022	Pan *et al.*, *Science 277*:815-818 (August 8, 1997) "An Antagonist Decoy Receptor and a Death Domain-Containing Receptor for TRAIL"
Ni Exhibit 2023	Pan *et al.*, *Science 276*:111-113 (April 4, 1997) "The Receptor for the Cytotoxic Ligand TRAIL"
Ni Exhibit 2024	Letter dated October 3, 2005 from Dr. Jorge Goldstein to Mr. Oliver Ashe
Ni Exhibit 2025	Letter dated October 12, 2005 from Dr. Jorge Goldstein to Mr. Oliver Ashe, with enclosed redacted copy of Material Transfer Agreement (MTA) between Human Genome Sciences and the University of Michigan and Amendment Nos. 1 to 9 of the MTA
Ni Exhibit 2026	Letter dated October 24, 2005 from Dr. Jorge Goldstein to Mr. Oliver Ashe
Ni Exhibit 2027	Letter dated October 6, 2005 from Mr. Oliver Ashe to Dr. Jorge Goldstein
Ni Exhibit 2028	Letter dated October 31, 2005 from Dr. Eldora Ellison to Dr. Guohua (James) Pan
Ni Exhibit 2029	Letter dated October 12, 2005 from Dr. Jorge Goldstein to Mr. Richard Brandon
Ni Exhibit 2030	Letter dated November 1, 2005 from Dr. Eldora Ellison to Mr. Richard Brandon
Ni Exhibit 2031	Emery *et al.*, *J. Biol. Chem. 273*:14363-14367 (1998) "Osteoprotegerin is a Receptor for the Cytotoxic Ligand TRAIL"
Ni Exhibit 2032	Continuity Data of U.S. Application No. 10/423,448, printed from the PTO's Public PAIR website
Ni Exhibit 2033	Notice of Allowance dated January 16, 2003, in Adams' U.S. Application No. 09/020,746
Ni Exhibit 2034	Transaction History of Ni U.S. Application No. 09/565,009; printed from the PTO's Public PAIR website
Ni Exhibit 2035	Transaction History of Adams U.S. Application No. 09/020,746; printed from the PTO's Public PAIR website
Ni Exhibit 2036	Miscellaneous Action dated May 1, 2003, in Adams' U.S. Application No. 09/020,746
Ni Exhibit 2037	October 23, 2003 Amendment and Under 37 C.F.R. §1.111 in Ni Application No. 09/565,009, assigned to Human Genome Sciences, Inc., containing the claims as pending on January 22, 2003
Ni Exhibit 2038	Miscellaneous Action dated November 12, 2003, in Adams' U.S. Application No. 09/020,746
Ni Exhibit 2039	Amendment and Supplemental Response submitted to Examiner Kaufman at the PTO by Party Adams on January 22, 2003, in its Application No. 09/020,746

Ni Exhibit #	*Description*
Ni Exhibit 2040	Declaration of Avi Ashkenazi under 37 C.F.R. §1.131 submitted to Examiner Kaufman at the PTO by Party Adams on January 22, 2003 in its Application No. 09/020,746, as an exhibit to its January 22,2003 Amendment and Supplemental Response
Ni Exhibit 2041	Supplemental Information Disclosure Statement and Forms 1449 listing the applications and references referred to in Party Adams' January 22, 2003 Amendment and Supplemental Reply, submitted to Examiner Kaufman at the PTO on January 22, 2003 by Party Adams in its Application No. 09/020,746
Ni Exhibit 2042	February 28, 2003 Second Supplemental Response, submitted to Examiner Kaufman at the PTO by Party Adams in its Application No. 09/020,746
Ni Exhibit 2043	May 1, 2003 PTO Communication regarding Adams' Application No. 09/020,746
Ni Exhibit 2044	Third Party Attempts to Protest or Otherwise Oppose the Grant of a Published Application, 1269 Off. Gaz. Office 179 (April 22, 2003)
Ni Exhibit 2045	February 14, 2005 Miscellaneous Communication to Examiner Kaufman at the PTO, containing assertions that if a patent issued from the Party Ni '009 application, it would be invalid; submitted by Party Adams in its Application No. 09/020,746
Ni Exhibit 2046	Party Adams' July 22, 2005 Amendment and Response to the Office Action dated March 16, 2005 in Application No. 10/423,448
Ni Exhibit 2047	Party Adams' July 19, 2005 Express Abandonment Under 37 C.F.R. § 1.138 of Application No. 09/020,746
Ni Exhibit 2048	Party Adams' July 22, 2005 Express Abandonment Under 37 C.F.R. § 1.138 of Application No. 10/207,295
Ni Exhibit 2049	Miscellaneous Action dated January 16, 2004, in Adams' U.S. Application No. 09/020,746
Ni Exhibit 2050	Letter to the USPTO Office of Enrollment and Discipline on behalf of Party Ni, reporting inappropriate conduct of Party Adams' counsel before the PTO during prosecution of U.S. Application No. 09/020,746
Ni Exhibit 2051	Maini *et al.*, *Clin. Exp. Rheumatol.* 12 Suppl 11:S63-6 (1994)
Ni Exhibit 2052	Feldmann *et al.*, *Cir Shock* 43:179-84 (1994)
Ni Exhibit 2053	Ware *et al.*, *J. Cell Biochem.* 60:47-55 (1996)
Ni Exhibit 2054	Ware *et al.*, *The Cytokine Handbook, Chapter 20*, pgs. 549-550 (1998)
Ni Exhibit 2055	Adams U.S. Application No. 08/857,216
Ni Exhibit 2056	Adams U.S. Provisional Application No. 60/046,615

Ni Exhibit #	***Description***
Ni Exhibit 2057	Adams Continuity Data page from public PAIR website for U.S. Application No. 09/020,746
Ni Exhibit 2058	Ni Application Data page from public PAIR website for U.S. Application No. 10/979,831
Ni Exhibit 2059	Ni Application Data page from public PAIR website for U.S. Application No. 10/774,622
Ni Exhibit 2060	Ni Application Data page from public PAIR website for U.S. Application No. 09/874,138
Ni Exhibit 2061	Ni Application Data page from public PAIR website for U.S. Appliction No. 10/648,825
Ni Exhibit 2062	Ni U.S. Appl. No. 60/040,846 (March 17, 1997 priority application)
Ni Exhibit 2063	Ni U.S. Appl. No. 60/054,021 (July 29, 1997 priority application)
Ni Exhibit 2064	Declaration of John C. Reed, M.D., Ph.D.
Ni Exhibit 2065	Chinnaiyan *et al.*, *Science* 274:990-992 (1996)
Ni Exhibit 2066	Marsters *et al.*, *Current Biology* 6:1669-1676 (1996)
Ni Exhibit 2067	Bodmer *et al.*, *Immunity* 6:79-88 (1997)
Ni Exhibit 2068	Office Action, mailed January 9, 2003 for Ni Appl. No. 09/565,009
Ni Exhibit 2069	Notice of Allowability, mailed January 21, 2005 for Ni Application No. 09/565,009
Ni Exhibit 2070	Miscellaneous Action dated July 16, 2004, in Adams' U.S. Application No. 09/020,746
Ni Exhibit 2071	*Curriculum vitae* of John C. Reed, M.D., Ph.D.
Ni Exhibit 2072	Tartaglia and Goeddel, *J. of Biol. Chem.* 267: 4304-4307 (1992)
Ni Exhibit 2073	Ni File History for U.S. Appl. No. 09/042,583 (March 17, 1998 priority application)
Ni Exhibit 2074	Ni File History for U.S. Appl. No. 60/132,498 (May 4, 1999 priority application)
Ni Exhibit 2075	Ni File History for U.S. Appl. No. 60/133,238 (May 7, 1999 priority application)
Ni Exhibit 2076	Ni File History for U.S. Appl. No. 60/148,939 (August 13, 1999 priority application)
Ni Exhibit 2077	Locksley, RM, *et al.*, *Cell* 104: 487 (2001)
Ni Exhibit 2078	Tartaglia, LA *et al.*, *Cell* 74: 845 (1993)
Ni Exhibit 2079	Wallach, D. *et al.*, *TIBS* 20: 342 (1995)
Ni Exhibit 2080	Itoh *et al. J., Biol. Chem.* 268: 10932 (1993)
Ni Exhibit 2081	Boldin, M.P. *et al.*, *J Biol Chem* 270: 387 (1995)
Ni Exhibit 2082	Kitson, J, *et al.*, *Nature* 384: 372 (1996) (*See* NX2159 for supplemented exhibit)

Ni Exhibit #	***Description***
Ni Exhibit 2083	Brutlag *et al.*, *Comp. Appl. Biosci.* 6:237-245 (1990)
Ni Exhibit 2084	Altschul *et al.*, *J Mol Biol.* 215(3):403-10 (1990)
Ni Exhibit 2085	Clewley *et al.*, *Methods Mol Biol.* 70:119-29 (1996)
Ni Exhibit 2086	Higgins *et al.*, *Gene* 73(1):237-44 (1988)
Ni Exhibit 2087	Devereux *et al.*, *Nucleic Acids Res.* 12(1 Pt 1):387-95 (1984)
Ni Exhibit 2088	Nakai and Kanehisa, *Genomics* 14:897-911 (1992)
Ni Exhibit 2089	Itoh, N. *et al.*, *Cell* 66: 233 (1991)
Ni Exhibit 2090	Yonehara, S *et al.*, *J. Exp. Med.* 169: 1747 (1989)
Ni Exhibit 2091	Trauth, B.C. *et al.*, *Science* 245: 301 (1989)
Ni Exhibit 2092	Cifone, MG *et al.*, *J. Exp. Med.* 177: 1547 (1993)
Ni Exhibit 2093	Tartaglia, L.A. *et al.*, *Proc. Natl. Acad. Sci.* 88: 9292 (1991)
Ni Exhibit 2094	Kohler and Milstein, *Nature* 256 (5517): 495-497 (1975)
Ni Exhibit 2095	Espevik T. *et al.*, *J. Exp. Med.* 171: 415 (1990)
Ni Exhibit 2096	Engelmann, H. *et al.*, *J. Biol. Chem.* 265: 14497 (1990)
Ni Exhibit 2097	Sheehan, K.C.F. *et al.*, *J. Exp. Med.* 181: 607 (1995)
Ni Exhibit 2098	Fadeel, B. *et al.*, *International Immunol.* 9: 201 (1997)
Ni Exhibit 2099	Alderson, M.R. *et al.*, *International Immunol.* 6: 1799 (1994)
Ni Exhibit 2100	Miscellaneous Action dated October 27, 2004, in Adams' U.S. Application No. 09/020,746
Ni Exhibit 2101	Examiner Interview Summary mailed April 18, 2005, in Adams' U.S. Application No. 09/020,746
Ni Exhibit 2102	Examiner Interview Summary mailed May 19, 2005, in Adams' U.S. Application No. 09/020,746

Ni Exhibit 2103	Examiner Interview Summary for interview conducted on February 13, 2003, in Adams' U.S. Application No. 09/020,746, assigned to Genentech
Ni Exhibit 2104	Electronic mail letter dated January 23, 2006 from Mr. Oliver Ashe to Dr. Eldora Ellison
Ni Exhibit 2105	Electronic mail letter dated November 7, 2005 from Mr. Richard Brandon to Dr. Eldora Ellison
Ni Exhibit 2106	Electronic mail letter dated November 17, 2005 from Mr. Richard Brandon to Dr. Eldora Ellison
Ni Exhibit 2107	Electronic mail letter dated January 23, 2006 from Mr. Richard Brandon to Dr. Eldora Ellison
Ni Exhibit 2108	Electronic mail letter dated November 17, 2005 from Ms. Linda Horner to Mr. Richard Brandon
Ni Exhibit 2109	Electronic mail letter dated January 20, 2006 from Dr. Eldora Ellison to Mr. Richard Brandon
Ni Exhibit 2110	Electronic mail letter dated January 24, 2006 from Mr. Richard Brandon to Ms. Linda Horner
Ni Exhibit 2111	Electronic mail letter dated January 24, 2006 from Mr. Oliver Ashe to Dr. Eldora Ellison
Ni Exhibit 2112	Letter dated January 19, 2006 from Mr. Richard Brandon to Ms. Linda Horner
Ni Exhibit 2113	Letter dated January 25, 2006 from Ms. Linda Horner to Ms. Patricia Thayer
Ni Exhibit 2114	All documents provided to HGS from the University of Michigan as of January 25, 2006
Ni Exhibit 2115	Letter dated January 26, 2006 from Ms. Patricia Thayer to Ms. Linda Horner
Ni Exhibit 2116	Non-Provisional Application Transmittal for U.S. Appl. No. 08/857,215, filed on May 15, 1997
Ni Exhibit 2117	U.S. Patent Appl. No. 08/857,216, filed January 16, 1996
Ni Exhibit 2118	Non-Provisional Application Transmittal for U.S. Appl. No. 09/020,746
Ni Exhibit 2119	U.S. Patent Appl. No. 09/020,746, filed February 9, 1998
Ni Exhibit 2120	Office Action issued on October 18, 2002 in U.S. Patent Appl. No. 09/020,746
Ni Exhibit 2121	Amendment and Response to October 18, 2002 Office Action, dated October 21, 2002, filed in U.S. Patent Appl. No. 09/020,746
Ni Exhibit 2122	Rule 131 Declaration signed by Avi Ashkenazi on October 15, 2002, filed in U.S. Appl. No. 09/020,746
Ni Exhibit 2123	Request for Correct Inventorship Under 37 C.F.R. § 1.48(b) dated October 21, 2002, filed in U.S. Appl. No. 09/020,746
Ni Exhibit 2124	Rule 131 Declaration signed by Avi Ashkenazi on January 17, 2003, filed in U.S. Appl. No. 09/020,746

Ni Exhibit 2125	Examiner's Amendment dated September 27, 2002, issued in U.S. Appl. No. 09/020,746
Ni Exhibit 2126	Electronic mail letter from Oliver Ashe to Eldora Lynn Ellison, dated January 20, 2006
Ni Exhibit 2127	Casaccia-Bonnefil et al., Nature 383: 716 (1996)
Ni Exhibit 2128	Frade et al., Nature 383: 166 (1996)
Ni Exhibit 2129	Carter et al., Neuron 18: 187-190 (1997)
Ni Exhibit 2130	Lippincott's Illustrated Reviews: Pharmacology 2nd Edition p.20 (1997) (*See* NX2156 for supplemented exhibit)
Ni Exhibit 2131	Stedman's Medical Dictionary 26th Edition p.38 (1995)
Ni Exhibit 2132	Essentials of Pharmacology, 2nd ed., p. 4 (1996) (*See* NX2158 for supplemented exhibit).
Ni Exhibit 2133	Basic Pharmacology p.15 (1996) (submitted at the deposition of March 20, 2006 as "Essentials of Pharmacology p. 15", *see* NX2143 and NX2157 for supplemented exhibits).
Ni Exhibit 2134	Bennett et al., J. Biol. Chem. 269(19): 14211 (1994)
Ni Exhibit 2135	Mark et al., J. Biol. Chem. 269(14): 10720 (1994)
Ni Exhibit 2136	Uckun et al., J. Biol. Chem. 266(26): 17478 (1991)
Ni Exhibit 2137	Armitage et al., Nature 357: 80 (1992)
Ni Exhibit 2138	Ogasawara et al., Nature 364: 806 (1993)
Ni Exhibit 2139	Suda et al., Cell 75: 1169 (1993)
Ni Exhibit 2140	Nagata et al., Science 267: 1449 (1995)
Ni Exhibit 2141	U.S. Application No. 60/072,481
Ni Exhibit 2142	Mühlenbeck et al., J. Biol. Chem. 275(41): 32208 (2000)
Ni Exhibit 2143	Basic Pharmacology, 4th ed., p.15 (1996)
Ni Exhibit 2144	Walczak et al., EMBO J 16(17): 5386 (1997)
Ni Exhibit 2145	MacFarlane et al., J. Biol. Chem. 272(41): 25417 (1997)
Ni Exhibit 2146	Wu et al., Nature Genetics 17: 141 (1997)
Ni Exhibit 2147	Herdegen et al., J Neuroscience 18(14): 5124 (1998)
Ni Exhibit 2148	Tewari et al., Curr Opin Gen Development 6: 39 (1996)
Ni Exhibit 2149	Hsu et al., Cell 84: 299 (1996)
Ni Exhibit 2150	Letter dated November 10, 2005 from Dr. Michael Karin to Dr. Vishva Dixit
Ni Exhibit 2151	Chuntharapai et al., J. Immunol. 166: 4891 (2001)
Ni Exhibit 2152	U.S. Appl. No. 2003/0004313
Ni Exhibit 2153	U.S. Patent No. 6,689,744

Ni Exhibit 2154	U.S. Patent No. 5,910,574
Ni Exhibit 2155	Electronic mail letter from Dr. Vishva Dixit to Dr. Michael Karin
Ni Exhibit 2156	Lippincott's Illustrated Reviews: Pharmacology 2nd Edition, Chapter 2: Pharmacokinetics and Drug Receptors p. 17-26 (1997)
Ni Exhibit 2157	Basic Pharmacology 4th Edition, Chapter 1: General Pharmacology p. 1-32 (1996)
Ni Exhibit 2158	Essentials of Pharmacology 2nd Edition, Chapter 1: General Principles and Pharmacokinetics p.1-33 (1996)
Ni Exhibit 2159	Mapara et al., Eur J Immunol 23: 702-708 (1993)
Ni Exhibit 2160	Kitson et al., Nature 384: 372 (1996)
Ni Exhibit 2161	Transcript of deposition of Dr. Michael Karin taken on March 20 and 21, 2006 (in two volumes, without errata sheets)
Ni Exhibit 2162	Videotaped copy of deposition of Dr. Michael Karin taken on March 20 and 21, 2006 (six disks)
Ni Exhibit 2163	Email from Vishva Dixit to John Reed, dated October 18, 2005
Ni Exhibit 2164	Morningstar Historical Stock Prices for Genentech, January 2, 2002 through March 30, 2006 (http://quicktake.morningstar.com/stock, visited 3/31/06)
Ni Exhibit 2165	Date-stamped cover sheet of the official transcript of the deposition of Dr. Michael Karin, dated 3/20/2006.
Ni Exhibit 2166	Date-stamped cover sheet of the official transcript of the deposition of Dr. Michael Karin, dated 3/21/2006.
Ni Exhibit 2167	Email from Oliver Ashe, Jr., counsel for Genentech, stating that he was unavailable for a phone conference with Judge Schafer on Friday, April 14, 2006.
Ni Exhibit 2168	Revised Transcript of July 27, 2006 Oral Argument

Respectfully submitted,

Jorge A. Goldstein
Attorney for Party Ni
Registration No. 29,021

Date: 9/14/06

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 New York Avenue, NW
Washington, D.C. 20005-3934

516663_1

CERTIFICATE OF SERVICE

I, Jorge A. Goldstein, hereby certify that a copy of the foregoing NI EXHIBIT LIST, along with any exhibits not previously served, has been served on the attorney of record of Party Adams and Party Rauch via FedEx on this 14th day of September 2006 addressed as follows:

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Respectfully submitted,

Jorge A. Goldstein
Attorney for Party Ni
Registration No. 29,021

Date: 9/14/06

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1100 New York Avenue, NW
Washington, D.C. 20005-3934

516663_1

EXHIBIT H

ORIGINAL

UNITED STATES PATENT AND TRADEMARK OFFICE

---X

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
(Administrative Patent Judge Richard E. Schafer)

---X

Human Genome Sciences, Inc.
Junior Party
(Patent 6,872,568;
Inventors: Jim Ni, Reiner L. Gentz, Guo-Liang Yu, Craig A. Rosen)

v.

Genentech, Inc.
Senior Party
(Application 10/423,448;
Inventors: Camillia W. Adams, Avi J. Ashkenazi, Anan Chuntharapai, Kyung Jin Kim).

---X

Patent Interference No. 105,361(RES)

---X

555 West Fifth Street
Conference Room, 40th Floor
Los Angeles, California 90013

March 20, 2006
9:34 a.m.

Videotaped Deposition of
MICHAEL KARIN, Ph.D.
Taken pursuant to Order and Notice,
before Paula A. Pyburn, CSR 7304/RPR.

ELLEN GRAUER COURT REPORTING CO. LLC
126 East 56th Street, Fifth Floor
New York, New York
212-750-6434
Ref: 80127

Adams EXHIBIT 1103
Ni v. Adams
Interference No. 105,361

EXHIBIT I

United States Patent and Trademark Office

Before the Board of Patent Appeals and Interferences
(Interference Trial Section)

13 September 2004

STANDING ORDER

This Order is promulgated by and for the Trial Section under Bd. R. 104 for use in contested cases.

CONTENTS

¶ 1 Notice of confidential information

Some opinions are selected for publication to promote public understanding of Trial Section practice or to create uniform practices. If a party believes that its application contains information not otherwise publicly available that should be redacted from any opinion, the party must **within two (2) months** of the initiation of the contested case file as a separate paper a notice specifically identifying such information.

If additional information not otherwise publicly available is introduced into a contested case that a party believes should be redacted from any opinion, the party must promptly file a notice specifically identifying the information.

If, after filing such notice, specifically identified information becomes publicly available (for example, through publication of a collateral application), the party shall promptly notify the Board of this change in the status of the information.

¶ 2 Record management

¶ 2.1 Letters between counsel not to be filed

No letter between counsel may be filed unless it is filed as an exhibit cited in a motion, opposition, or reply, or during cross-examination.

¶ 2.2 No duplicate papers

A party may not file (not even as an appendix or exhibit) a copy of a paper previously filed in the same contested case.

¶ 3 Mandatory notices

¶ 3.1 Real party-in-interest

Within **fourteen (14) days** of the date of the Declaration, each party must file as a separate paper a notice of any and all right, title, or interest in any application or patent involved in the contested case.

¶ 3.2 Related proceedings

Within **fourteen (14) days** of the initiation of a contested case, each party must file and serve as a separate paper a notice identifying the application or patent number of every United States application or patent claiming, or which may claim, the benefit of priority of the filing date of the party's involved patent or application. If there are no such applications or patents the notice must state this fact. If, during the course of the proceeding, a party files an application claiming, or which may claim, the benefit of the filing date of an involved application or patent, a notice of the filing, including the application number, must be promptly served and filed.

¶ 4 Communications with the Board

¶ 4.1 Default mode

Mail is the default mode of communication.

¶ 4.2 Filing by hand

Hand delivery to the Board must occur between the hours of 8:30 a.m. and 5:00 p.m at:[*]

Madison Building East, 9th Floor
600 Dulany Street
Alexandria, Virginia 22314

Any paper hand-delivered directly to the Board before 10:00 a.m. is deemed to have been filed the previous business day provided the paper was properly served the previous business day.

¶ 4.3 Overnight delivery services

Papers filed using an overnight delivery service must be addressed:[**]

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* Prior to 6 October 2004, deliver to Crystal Gateway Two, Floor 10, 1225 South Clark Street, Arlington, Virginia.

** Prior to 6 October 2004, use Board of Patent Appeals and Interferences, Crystal Gateway Two, Floor 10, 1225 South Clark Street, Arlington, Virginia.

Board of Patent Appeals and Interferences
Madison Building East, 9th Floor
600 Dulany Street
Alexandria, Virginia 22314

Properly addressed papers filed are deemed filed on the date they are delivered to the overnight delivery service.

¶ 4.4 Telephone calls

Telephone calls to the Board regarding a contested case must be placed to 571-272-9797.[*] A telephone call requesting a conference call must be directed to Trial Section support staff.

¶ 4.5 Facsimile

The facsimile number for contested cases is 571-273-0042.[**] Do not send papers exceeding five (5) pages in length without prior permission from Trial Section support staff.

¶ 5 Copies of authority cited

If a party files a paper citing an authority that is not reported in (1) United States Reports or West Publishing Company's Supreme Court Reporter, (2) the second or third series of West's Federal Reports, or (3) the first or second series of the Bureau of National Affairs' United States Patents Quarterly, then the party must file and serve a copy of the authority.

¶ 6 Modification of the Standing Order

An administrative patent judge may modify the terms of this Order.

¶ 7 Paper format

¶ 7.1 Footnotes

The use of footnotes is discouraged. Footnotes must be double-spaced.

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* Prior to 6 October 2004, use 703-308-9797.

** Prior to 6 October 2004, use 703-305-0942.

¶ 7.2 Cover sheet for papers other than exhibits

¶ 7.2.1 Caption

The heading shown in Part G of the Declaration shall be used in all papers other than exhibits. Form **1** in the Appendix of Forms shows a standard caption for an interference.

¶ 7.2.2 Style

The style of each paper must appear on a single line and must not use the words "et al". Styles for papers other than motions, oppositions, and replies should be simple and descriptive.

¶ 7.2.3 Color of cover sheet

The first page of all papers filed in an contested case must be **pink** similar to the pink first page of the Declaration.

¶ 7.3 Combined oppositions and replies not to be filed

An opposition shall respond to only a single motion and a reply shall respond to only a single opposition.

¶ 7.4 Copy for the administrative patent judge

A party must file (1) an original and (2) a copy of each paper filed. The copy shall be marked at the top:

APJ COPY

¶ 8 Papers in electronic form

¶ 8.1 Only a copy of a paper may be filed in electronic form

Parties may file a copy of a paper in electronic form. (A facsimile is not a paper in electronic form.) The required number of paper copies must also be filed with the Board and served on all opponents.

¶ 8.2 Format

The Board can accept electronic copies in the following PC-compatible media:

A compact disc,

3¼ inch diskette,

A 100 MB Zip® disk, or

A 2 GB Jaz® disk.

The electronic copy must be capable of:

(a) Operating on a computer running WINDOWS XP.

(b) Displaying on a monitor set to display at 256 colors on an 800 x 600 pixel screen setting.

(c) Opening and being word searched in ADOBE ACROBAT READER, WORDPERFECT 9, or MICROSOFT WORD 2000. Parties use other formats at their own risk.

The file name of each electronic document must concisely identify the content of the document (e.g., Jones PM1.wpd, Smith Opp1.doc; Ex1038.pdf). If a hearing is requested, four copies of the electronic media should be filed with the Board and one copy served on each opponent.

¶ 9 Service

¶ 9.1 Alternatives to EXPRESS MAIL®

Any other mode of service that accomplishes a same-day or overnight delivery of the paper (e.g., by hand, facsimile, or a commercial overnight delivery service) may be substituted for EXPRESS MAIL® service.

¶ 9.2 Papers served but not filed

The following papers must be served on an opponent, but should not be filed with the Board at the time of service:

(a) An objection to the admissibility of evidence.

(b) A notice requesting cross-examination.

(c) Automatic discovery pursuant to Bd. R. 150(b)(1).

Such papers may be filed later as an exhibit if a dispute arises with respect to the paper served.

¶ 9.3 Transmittal sheets

Do not file a transmittal sheet listing papers being filed except an exhibit list may be filed when more than one exhibit is being filed.

¶ 10 Lead and backup counsel

The notice identifying counsel under Bd. R. 108(b) must identify both a lead counsel and a backup lead counsel, and must provide for each the contact information specified in Bd. R. 108(b)(1)-(b)(5).

If lead counsel or backup counsel are not counsel of record (37 CFR § 1.34(b)) in the involved application or patent, then a power of attorney must be filed with the Board for entry in the involved patent or application file within the **fourteen (14) day** period of Bd. R. 108(b).

¶ 11 Request for file copies

A party seeking copies of an involved or benefit file mentioned in the Declaration must, within **fourteen (14) days** of the date of the Declaration, file with the Board (not another part of the Office) a separate paper styled [Name of party] REQUEST FOR FILE COPIES to which is attached a completed FILE COPY REQUEST. See Form **4** in the Appendix of Forms.

¶ 12 Later presented or contested claims

If a party moves to involve a new (or uninvolved) claim in the contested case, the movant must comply with the requirements of Bd. R. 110(a) and (b) for the new claim.

¶ 13 Motions

¶ 13.1 Numbering motions

Each motion of each party must be numbered consecutively, starting with one, regardless of the type of motion.

¶ 13.2 Page limits in motions

A motion is limited to twenty-five (25) pages, not including a table of contents, a table of authorities, and the certificate of service.

¶ 13.3 Format

Each motion shall set out in the following order:

(a) The precise relief requested.

(b) The evidence (i.e., a list in numerical order of all exhibits) the movant cites in support of the motion with a brief description of
the exhibit (e.g., "Exhibit 1038, Second Declaration of Jones").

(c) A statement of facts in separately numbered paragraphs sufficient to establish entitlement to the requested relief, with citations to the evidence.

(d) An argument setting out the reasons why relief should be granted.

¶ 13.4 Statement of material facts

Facts should be set out as short, numbered declaratory sentences that are capable of being admitted or denied.

Citation to the evidence must be specific, e.g., (1) by column and line of a patent, (2) page, column and paragraph of a journal article and (3) page and line of a cross-examination deposition transcript.

¶ 13.5 Claim chart alternative

As an alternative to a claim chart, a party may reproduce the complete claim in the appendix. Following each limitation in the claim, and within braces { }, insert in bold a specific citation to the information to be compared to the limitation (such as where a prior art reference describes the limitation). Braces { } must be used instead of brackets [ ] because brackets are used to indicate amended portions of claims in reissue applications.

¶ 14 Oppositions and replies

¶ 14.1 Numbering oppositions and replies

Each opposition and reply must use the number of the motion to which it corresponds.

¶ 14.2 Page limits in oppositions and replies

An opposition is limited to twenty-five (25) pages, and a reply is limited to ten (10) pages, not including a table of contents, a table of authorities, and any certificate of service.

¶ 14.3 Opposition format

Each opposition shall set out in the following order:

(a) The evidence (i.e., a list in numerical order of all exhibits by number) the opponent cites in support of the opposition.

(b) For each material fact alleged in the motion, a concise statement admitting, denying, or stating that the opponent is unable to admit or deny the fact.

(c) Any additional material fact upon which the opposition relies, with a citation to the evidence. Any additional material fact must be consecutively numbered beginning with the next number after the last numbered material fact.

(d) An argument stating the reason why relief is opposed shall be made in the following manner:

> On page x, lines y-z of the motion, it is argued (or stated factually) that _. The response is _.

¶ 14.4 Reply format

Each reply shall set out in the following order:

(a) The evidence (i.e., a list in numerical order of all exhibits by number) the movant cites for the first time in support of the reply.

(b) For each material fact alleged in the opposition, a concise statement admitting, denying, or stating that
the movant is unable to admit or deny the fact.

(c) Any additional material fact upon which the movant relies to rebut the opposition, with a citation to the evidence and an explanation as to why each additional material fact was not set out in the motion. Any additional material fact must be consecutively numbered beginning with the next number after the last numbered material fact.

(d) The argument responsive to statements in the opposition shall be made in the following manner:

> On page x, lines y- z of the opposition, it is argued (or stated factually) that _. The response is _.

¶ 15 Miscellaneous motions

¶ 15.1 Mandatory conference call

Before filing a miscellaneous motion, a party must:

(a) confer with all opponents and,

(b) if agreement cannot be reached, arrange a conference call to the Board official administering the contested case.

¶ 15.2 Timeliness

The movant must explain why the motion is timely.

¶ 16 Oral argument

¶ 16.1 Demonstrative exhibits

Four copies (one for the record and one for each judge) of each demonstrative exhibit must be filed or be presented at oral argument. Demonstrative exhibits must be served in advance. Bd. R. 124(d).

Any special equipment needed for oral argument is the responsibility of the party needing the equipment.

¶ 16.2 Transcript of oral argument

When an argument is to be transcribed, the party should notify Trial Section support staff personnel at least one business day prior to oral argument so that arrangements may be made in the hearing room for the reporter.

The court reporter shall use a stenography machine and may also use a tape recording device as a backup. Microphones at individuals' locations are not authorized.

The party requesting transcription must arrange for the transcription and pay the costs. Parties are encouraged to share the costs.

¶ 17 Request for rehearing

¶ 17.1 Form for request

A request for rehearing of decision must set out in the following order:

(a) The evidence (i.e., a list in numerical order of all exhibits by number) that the party believes was overlooked or misapprehended.

(b) The argument responsive to the decision shall be made with particularity in the following manner:

> On page _, lines _-_, the decision states _. The decision is believed to have overlooked [or misapprehended] _. This point was set forth in _ Motion [or Opposition or Reply] _ at page _, lines _-_.

¶ 17.2 Number of requests

A party may file no more than one request for rehearing per motion decision.

¶ 18 Settlement discussions required

¶ 18.1 Last-named party initiates

The party named last on in the caption set in the declaration is responsible for (1) initiating any settlement discussions, (2) initially drafting any document and (3) initiating any conference call required by this paragraph. The parties may agree to permit another party to undertake the obligations placed upon the last-named party.

¶ 18.2 Initial conference

Within **three (3) months** of the date of the Declaration, the parties must conduct a settlement conference and must initiate a conference call with the Board official assigned to the case. During the call, the parties should be prepared to report:

(a) the outcome of the settlement discussion;

(b) whether the parties are actively engaged in settlement negotiations and, if so, what steps have already been taken toward settlement;

(c) whether any settlement negotiations are directed toward obviating the need for filing motions;

(d) any issues that are not subject to settlement negotiations; and

(e) the status of any settlement negotiations, including how much time might be needed to conclude those negotiations.

¶ 18.3 Subsequent conferences

Unless a different time is set in an order, within **two (2) months** after a panel decision on substantive motions, the parties must conduct another settlement conference and initiate another conference call with the Board on the conference as provided in the preceding paragraph of this order.

¶ 18.4 Filing notice of conferences

Prior to initiating any conference call required by this paragraph, the parties must file (preferably by facsimile) a joint statement indicating that a good faith effort has been made to settle the contested case.

¶ 19 Admissibility of specification

A specification of an involved application or patent is admissible as evidence only to prove what the specification or patent describes. If there is data in the specification upon which a party intends to rely to prove the truth of the data, an affidavit by an individual having first-hand knowledge of how the data was generated (i.e., the individual who performed an experiment reported as an example in the specification) must be filed. This individual may be cross examined.

¶ 20 Form of evidence

¶ 20.1 Papers in a patent or application file

¶ 20.1.1 Reliance on a portion of a file

If a motion relies on any paper in the file of an involved or benefit patent or application (including a specification or drawings), a copy of the entire paper shall be made an exhibit in the contested case. Do not submit an entire application file as a single exhibit.

¶ 20.1.2 No exception for affidavits

An affidavit filed during *ex parte* prosecution of an involved or benefit application or patent is not automatically in evidence. A party seeking to have such an affidavit considered must place the affidavit in evidence. Each opponent will have an opportunity to object to the admissibility of the evidence and may cross examine the affiant. The party submitting the evidence will have an opportunity to supplement the evidence following a timely objection by an opponent. Bd. R. 155(b)(2).

¶ 20.2 Exhibit labels

¶ 20.2.1 Unique and consecutive

Each exhibit from a party must be uniquely and consecutively numbered within the range the Board assigns to the party for the proceeding.

Unless otherwise provided in an order, the party named last in the caption set in the declaration is assigned the range 1001-1999, while the first-named party is assigned 2001-2999.

¶ 20.2.2 Material covered on first page

If an exhibit label covers important material on the first page of an exhibit, a copy of the first page of the exhibit must be reproduced and presented as page 1-a of the exhibit.

¶ 20.3 Filing of exhibits

A set of original exhibits must be filed in a box, an accordion folder, or a comparable folder containing the exhibits in numerical order, separated by a divider that conspicuously identifies each exhibit by number.

If any party requests oral argument, three (3) separate additional sets of exhibits must also be filed; otherwise, one (1) additional set of exhibits must be filed.

¶ 20.4 Exhibit list

A current list shall be served whenever evidence is served.

The exhibit list shall be filed with the exhibits.

¶ 21 Objections

¶ 21.1 Objecting to served evidence

An objection to the admissibility of evidence should not be filed except as part of a motion to exclude.

¶ 21.2 Serving supplemental evidence

Supplemental evidence responding to an objection to the admissibility of evidence should not be filed until it is used as an exhibit.

¶ 21.3 Motion to exclude evidence

(a) A motion to exclude evidence shall:

(1) identify where in the record the objection was originally made,

(2) identify where in the record the evidence to be excluded was relied upon by an opponent, and

(3) address objections to exhibits (in whole or in part) in exhibit numerical order.

(b) When a timely objection has been made (see SO ¶ **21.1**), no conference call is necessary to file a motion to exclude.

¶ 22 Cross examination

¶ 22.1 Time for cross examination

The party relying on an affiant must make the affiant available for cross examination during the time required by this Order. The parties must confer to reach agreement on dates and times for cross examination of witnesses.

¶ 22.1.1 Start date

Unless the parties otherwise agree, cross examination of an affiant may begin no earlier than twenty-one (21) days after service of the affidavit.

¶ 22.1.2 End date

Unless the parties otherwise agree,

(1) Cross examination of affiant relied upon in a motion other than a miscellaneous motion must occur at least ten (10) days before the opposition to the motion is due.

(2) Cross examination of an affiant relied upon in an opposition to a motion other than a miscellaneous motion shall take place at least ten (10) days before a reply is due.

¶ 22.2 Notice

A notice requesting cross examination shall be served (but need not be filed).

¶ 22.3 Proponent responsible.

The party relying on an affiant is responsible for securing the services of a court reporter and providing a copy of any transcript to every opponent.

¶ 22.4 Order of cross examination

While a party requesting cross examination may choose the order of the witnesses, Bd. R. 157(c)(2), order must be reasonable.

¶ 22.5 Filing transcript

An uncertified copy of each deposition transcript must be filed as an exhibit. A certified transcript of testimony need not be filed unless required by the Board.

¶ 22.6 Cross examination guidelines

The cross examination guidelines appended to this Order apply to all cross examination in this contested case.

¶ 22.7 Observations on cross examinations

Cross examination may occur after a party has filed its last substantive paper on an issue (e.g., after the reply) and result in testimony that should be called to the Board's attention but does not merit a motion to exclude. The Board may authorize the filing of observations to identify such testimony and responses to observations.

An observation must be a concise statement of the relevance of precisely identified testimony to a precisely identified argument or portion of an exhibit (including another part of the same testimony). Any response should be equally concise. An

observation (or response) is not an opportunity to raise new issues, to re-argue issues, or to pursue objections. Each observation should be in the following form:

In exhibit _, on page _, lines_, the witness testified _. This testimony is relevant to the _ on page _ of _. The testimony is relevant because _.

The entire observation should not exceed one short paragraph.

¶ 23 Expert testimony on patent law

Affidavits of patent law experts on issues of law generally will not be admitted in evidence.

¶ 24 Explaining tests and data

Any explanation should take place through affidavit testimony of a witness, preferably accompanied by citation to relevant pages of standard texts (which should be filed as exhibits).

¶ 25 Adding an application or patent

A suggestion to add an application or patent to an interference must be in the form of a miscellaneous motion. Bd. R. 121(a)(3). The motion must:

(a) identify the application or patent to be added;

(b) certify that a complete copy of the file wrapper for the application or patent has been served on all opponents;

(c) indicate which claims of the patent or application should be designated as corresponding to the count; and

(d) explain whether there are alternative remedies; if so, why alternative remedies are not adequate; and what attempts, if any, have been made to have the examiner recommend declaration of another interference involving the application or patent sought to be added to the interference.

¶ 26 Motions list

All substantive and anticipated responsive motions must be listed on the motions list. No other substantive motions may be filed without prior Board authorization obtained during a conference call.

¶ 27 Notice under 35 U.S.C. 135(c)

Notice is hereby given of the requirement of 35 U.S.C. 135(c) for filing in the Office a copy of any agreement "in connection with or in contemplation of the termination of the interference."

¶ 28 Specific substantive motions

¶ 28.1 Obviousness

When obviousness (35 U.S.C. 103) is the basis for a motion for judgment, if a reference does not teach or suggest a limitation, that fact must be explicitly identified as a difference in the statement of material facts. The argument portion of the motion must account for the difference.

An explanation must be made in the body of the motion (not an appendix) why the subject matter of the claim, as a whole, would have been obvious to a person having ordinary skill in the art notwithstanding any difference.

¶ 28.2 Inequitable conduct

A motion alleging inequitable conduct must make out a *prima facie* case of inequitable conduct or fraud. Additional discovery (Bd. R. 150(c)) or a request to take testimony (Bd. R. 156), asserted to be necessary to make out a *prima facie* case, will rarely be authorized. An allegation of inequitable conduct or fraud that fails to make out a *prima facie* case may result in sanctions or a referral to the Office of Enrollment and Discipline.

¶ 28.3 Adding a reissue application

A movant seeking to add its own reissue application must stipulate that every added or amended claim (compared to the original patent) corresponds to a count in the interference. If the reissue application has not been filed in the Office, it must be filed directly with the Board.

Entered on 13 September 2004

GARY V. HARKCOM, Acting Chief Administrative Patent Judge	
FRED E. M^C^KELVEY Senior Administrative Patent Judge	
RICHARD E. SCHAFER Administrative Patent Judge	
JAMESON LEE Administrative Patent Judge	
RICHARD TORCZON Administrative Patent Judge	
CAROL A. SPIEGEL Administrative Patent Judge	BOARD OF PATENT APPEALS AND INTERFERENCES
SALLY GARDNER LANE Administrative Patent Judge	
SALLY C. MEDLEY Administrative Patent Judge	
MICHAEL P. TIERNEY Administrative Patent Judge	
JAMES T. MOORE Administrative Patent Judge	
LINDA R. POTEATE Administrative Patent Judge	
MARK NAGUMO Administrative Patent Judge	

APPENDIX OF FORMS

Form 1. Standard caption for an interference

Filed on behalf of: [Name of filing party]

By: [Name of lead counsel]
[Name of backup counsel]
[Street address]
[City, State, and ZIP Code]
[Telephone number]
[Facsimile number]

Paper No. [leave blank]

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge [Surname of administrative patent judge])

[Name of junior party]
([Involved application or patent number])
Junior Party,

v.

[Name of Senior party]
([Involved application or patent number])
Senior Party.

Patent Interference No. [interference number]

[TITLE OF PAPER]

Form 2. Typical schedule for motions

These times typically can be changed by stipulation

TIME PERIOD 1 . . . . 6 weeks
File substantive motions
File (but serve one week later) priority statements

TIME PERIOD 2 . . . . 3 weeks
File responsive motions to motions
filed in TIME PERIOD 1

TIME PERIOD 3 . . . . 6 weeks
File oppositions to all motions

TIME PERIOD 4 . . . . 6 weeks
File replies

TIME PERIOD 5 . . . . 6 weeks
File request for oral argument
File motions to exclude
File observations

TIME PERIOD 6 . . . . 3 weeks
File oppositions to motions to exclude
File response to observations

These times cannot be changed by stipulation

TIME PERIOD 7 . . . . 2 weeks
File replies to oppositions to motions to exclude

TIME PERIOD 8 . . . . 1 week
File exhibits
File sets of motions

Form 3. Typical schedule for priority motions in an interference

These times typically can be changed by stipulation

TIME PERIOD 9 . . . . 6 weeks
<u>Junior party only</u> file priority brief and serve
(but do not file) priority evidence

TIME PERIOD 10 . . . . 6 weeks
<u>Senior party only</u> file priority brief and serve
(but do not file) priority evidence

TIME PERIOD 11 . . . . 6 weeks
File opposition to priority briefs
Serve (but do not file) opposition evidence

TIME PERIOD 12 . . . . 6 weeks
File reply
Serve (but do not file) reply evidence

TIME PERIOD 13 . . . . 6 weeks
Request hearing
File list of issues to be considered
File observations
File motion to exclude

TIME PERIOD 14 . . . . 3 weeks
File response to observations
File opposition to motion to exclude

The last time cannot be changed by stipulation

TIME PERIOD 15 . . . . 2 weeks
File reply to opposition to motion to exclude

TIME PERIOD 16 (Last Time) . . . . 1 week
File and serve the exhibits
File sets of priority motions

Form 4. File copy request

FILE COPY REQUEST
Contested Case No. [Contested Case number]

Attach a copy of section E of the DECLARATION to this REQUEST. On the copy, circle each patent and application that you are requesting.

Include the following information to facilitate processing of this REQUEST:

1. Charge fees to USPTO Deposit Account No. ______________________________

2. Complete address, including street, city, state, zip code and telephone number (do not list a Post Office box because file copies are sent by commercial overnight courier).

____

____

____

____

3. Telephone, including area code: ______________________________________

APPENDIX: CROSS EXAMINATION GUIDELINES

Introduction

Cross examination can be a useful tool for determining the facts in a case. In contested cases, direct testimony is usually presented by affidavit, Bd. R. 157(a), while cross examination occurs by oral deposition. Bd. R. 157(b).

Cross examination should be a question-and-answer conversation between the examining lawyer and the witness. The defending lawyer must not act as an intermediary, interpreting questions, deciding which questions the witness should answer and helping the witness formulate answers. The witness comes to the cross examination to be questioned. It is the witness, and not the lawyer, who is testifying.

The cross-examination guidelines below are essentially the deposition guidelines set out in *Hall v. Clifton Precision*, 150 F.R.D. 525 (E.D. Pa. 1993) (Gawthrop, J.) The only significant difference, which results from Bd. R. 157(e)(4), is that certain objections must be noted on the record.

Failure to adhere strictly to these guidelines may be a basis for a sanction under Bd. R. 128, which could include a requirement that the witness, on very short notice may be directed to appear before the Board or elsewhere, as may be appropriate, coupled with any appropriate award of compensatory damages under Bd. R. 128(b)(6). In addition, cross examination undertaken contrary to these guidelines may result in exclusion of an affidavit from evidence or in the assignment of little, if any weight, to the direct testimony of a witness who was cross examined.

Guideline [1]

At the beginning of a cross examination, the party conducting the cross examination must instruct the witness on the record to ask deposing counsel, rather than the witness's own counsel, for clarifications, definitions or explanations of any words,

questions or documents presented during the cross examination. The witness must follow these instructions.

Guideline [2]

A party may not direct or request that a witness not answer a question unless:

(a) a party has objected to the question on the ground that the answer would:

(1) reveal privileged material or

(2) violate a limitation the Board has imposed and

(b) counsel immediately places a conference call to the Board official assigned to the contested case asking for a ruling on the objection.

Under these circumstances, (i) the cross examination shall be suspended, (ii) the conference call immediately shall be placed to the Board official assigned to the contested case, and (iii) all counsel must be prepared to explain their respective positions during the call. The court reporter for the cross examination shall be available to record the conference call and to read back questions to which an objection has been made.

If the Board cannot be reached, then the party directing a witness not to answer shall, within **two (2) business days**, deliver by hand (SO ¶ **4.2**), overnight service (SO ¶ **4.3**), or facsimile (SO ¶ **4.5**) directly to the Board, and not to the Office Mail Room or any other part of the Office, a miscellaneous motion seeking relief. Bd. R. 121(a)(3). Any opposition must be hand delivered to the Board within **two (2) business days** of service of the motion. While a reply can be filed, the motion is likely to be decided before it is filed.

Guideline [3]

Counsel must not make objections or statements that even remotely suggest an answer to a witness. Any objection to evidence during cross examination must be stated concisely and in a non-argumentative and non-suggestive manner and must include the legal basis for the objection. Examining counsel must not address the correctness of an objection, but may instead continue with questions to the witness, the objection having been noted on the record as required under Bd. R. 157(e)(4).*

Guideline [4]

Counsel and their witness-clients shall not engage in private, off-the-record conferences during cross examinations or during breaks or recesses, except for the purpose of deciding whether to assert a privilege.**

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* With respect to this guideline, the following observation by Judge Gawthrop, 150 F.R.D. at 530 n.10, is highly relevant:

> I also note that a favorite objection or interjection of lawyers is, "I don't understand the question; therefore the witness doesn't understand the question." This is not a proper objection. If the witness needs clarification, the witness may ask the deposing lawyer for clarification. A lawyer's purported lack of understanding is not a proper reason to interrupt a deposition. In addition, counsel are not permitted to state on the record their interpretations of questions, since those interpretations are irrelevant and often suggestive of a particularly desired answer.

By way of example, the following comments by defending counsel generally are viewed as suggesting an answer to a witness:

(a) Objection, vague.
(b) Objection to the form of the question.
(c) Take your time in answering the question.
(d) Look at the document before you answer.
(e) Counsel, do you want to show the witness the document?

** The term "witness-clients" in the context of this guideline includes all witnesses who are employed by, or otherwise under the control of, the real party-in-interest, including retained expert witnesses, as well as the individual or individuals named in the caption of the contested case. With respect to this guideline, the following observation by Judge Gawthrop, 150 F.R.D. at 528, is highly relevant:

> The fact that there is no judge in the room to prevent private conferences does not mean that such conferences should or may occur. The underlying reason for preventing private conferences is still present: they tend, at the very least, to give the appearance of obstructing the truth.

Guideline [5]

Any conferences that occur pursuant to, or in violation of, guideline [4] are a proper subject for inquiry by deposing counsel to ascertain whether there has been any witness-coaching and, if so, the nature of that coaching.

Guideline [6]

Any conferences that occur pursuant to, or in violation of, guideline [4] shall be noted on the record by the counsel who participated in the conference. The purpose and outcome of the conference shall also be noted on the record.

Guideline [7]

Counsel taking cross-examination shall provide to defending counsel a copy of all documents shown to the witness during the cross examination. The copies shall be provided either before the cross examination begins or contemporaneously with the showing of each document to the witness. The witness and defending counsel do not have a right to discuss documents privately before the witness answers questions about the documents.

APPENDIX: INDEX OF TIMES

Times running from initiation/declaration

Default times before a triggering event

Index of Times

Default times after a triggering event